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MARGINAL PERCENTAGES IN MULTIWAY TABLES OF QUANTAL DATA WITH DISPROPORTIONATE FREQUENCIES

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SUMMARY

When multiway tables of quantal data are analysed by transforming the percentages and fitting constants to the transformed variate by the method of maximum likelihood, direct inverse transformation of the values of the fitted constants gives percentages which may deviate widely from those observed. The reasons for this are explained and methods are given for obtaining correct percentages.

INTRODUCTION

Transformations, such as the logit and log log, are now being used increasingly for the analysis of multiway tables of quantal data. The basic procedures have been described by Jolly [1950], Dyke and Patterson [1952] and Yates [1955]. Their earlier use for this purpose was undoubtedly inhibited by the heavy numerical computation required, but the burden of this has been greatly lightened by the introduction of electronic computers. The Rothamsted computer, for example, has a programme for analyses of this type which will handle tables with up to five factors in which the number of cells and marginal means does not exceed 256. Constants representing the main classifications and any desired sets of sub-classifications can be fitted, and the values of the constants and the reduction in variance are determined.

When an analysis of this kind has been completed, it is frequently desirable to present the results in terms of percentages, instead of, or as well as, in terms of the transformed variate. If the constants obtained in the analysis are retransformed directly to percentages, considerable distortions may occur. It is the purpose of this paper to explain why such distortions arise and how they may be removed.

ESTIMATION OF A MEAN PERCENTAGE BY MEANS OF A TRANSFORMATION

It is well known that, if a set of percentages is transformed by a non-linear transformation such as the logit transformation, and the

mean of the transformed values is retransformed back to a percentage, this percentage will not equal the mean of the original percentages. The ordinary maximum likelihood procedure of fitting, using provisional and working values and successive approximation, removes this distortion.

This result follows immediately from the fact that the weighted mean of a set of percentages, with weights proportional to the frequencies, is the maximum likelihood estimate of the mean percentage. A direct proof may, however, be of interest, and illustrates the procedure to be followed in the more complicated case of two-way tables, discussed in the next section.

Suppose we have a set of proportions $p_r = x_r/n_r$, where n_r is the number of observations in class r and x_r the number of those fulfilling the required condition, so that $100\ p_r$ is the corresponding percentage.

If the observations in all the classes are in fact samples from the same population, the sufficient estimate of the population proportion is

$$\hat{p} = \sum x_r / \sum n_r = \sum n_r p_r / \sum n_r .$$

If, with any transformation $y = f(p)$, with inverse $p = F(y)$, a common provisional value Y is taken, and Y_{max} and Y_{min} are the maximum and minimum values and w the weighting coefficient for this value of Y (as defined in the ordinary maximum likelihood procedure), then the working value for class r will be

$$y_r = p_r Y_{max} + q_r Y_{min} .$$

The weighted mean of these values, which will provide a first estimate of the adjusted mean, and also a new provisional value, will be

$$Y' = \frac{\sum n_r w y_r}{\sum n_r w} = \frac{\sum n_r p_r}{\sum n_r} Y_{max} + \frac{\sum n_r q_r}{\sum n_r} Y_{min}$$

$$= \hat{p} Y_{max} + \hat{q} Y_{min} .$$

If successive approximations are now carried out until there is no change in the provisional value, we shall arrive finally at the equations

$$\begin{aligned} Y &= \hat{p} Y_{max} + \hat{q} Y_{min} , \\ \hat{y} &= Y, \end{aligned} \tag{1}$$

where Y, Y_{max} and Y_{min} are the final values of Y' and the corresponding maximum and minimum. If $P = F(Y)$, the formulae for Y_{max} and Y_{min} are

$$Y_{\max} = Y + Q\frac{dY}{dP},$$

$$Y_{\min} = Y - P\frac{dY}{dP}.$$

(See, for example, Fisher and Yates [1957], p. 14.) Hence equation (1) reduces to $\hat{p}Q - \hat{q}P = 0$, i.e. $P = \hat{p}$, and therefore $\hat{p} = F(\hat{y})$. In other words the inverse transformation of the maximum likelihood estimate $\hat{y}$ gives an estimate $\hat{p}$ which is equal to the weighted mean of the original percentages, with weights proportional to the frequencies.

TWO-WAY TABLES

In the analysis of a multi-way table of quantal data the expected values of the transformed variate are assumed to be made up of additive components representing the various classifications which require to be taken into account.

Thus in an $R \times S$ two-way table the expected value of the transformed variate for the cell (r, s) is given by

$$\hat{y}_{r\cdot} = m + a_r + b_\cdot ,$$

where m is a general mean, $a_1 , \cdots , a_r$ is the set of constants for the first classification, and $b_1 , \cdots , b_\cdot$ the set for the second classification. The values of m and the a's and b's are obtained by the maximum likelihood fitting.

If the $\hat{y}_{r\cdot}$ are transformed back to percentages $100\,\hat{p}_{r\cdot}$, then $100\,\hat{p}_{r\cdot}$ will represent the expected percentages on the assumed hypothesis without distortion. Examination of the equations which are used to determine the fitted constants, on the lines of the last section, shows that in the case of the logit transformation the weighted means of $\hat{p}_{r\cdot}$, with weights equal to the original frequencies, will reproduce the marginal percentages of the original table exactly. This depends on the fact that for this transformation

$$w\frac{dY}{dP} = \text{const},$$

which follows from the general formula for w, namely

$$w = \frac{1}{PQ}\left(\frac{dP}{dY}\right)^2.$$

With other transformations there will be some discrepancy. There is, however, no real inconsistency; the marginal percentages so obtained,

not those observed, are the appropriate estimates of these percentages for the adopted model, with the observed weights.

To represent the estimates of the class-differences in terms of percentages in compact form, we require the expected percentages of the margins of the table with some form of proportionate weights. As in the quantitative case it is usually best to give the percentages that would be expected if the frequencies in the cells of the table were proportionate to the marginal frequencies, i.e.

$$n'_{rs} = n_{r.}n_{.s}/n_{..} ,$$

where

$$n_{r.} = \sum_{s} n_{rs} , \quad \text{etc.}$$

These percentages can be computed directly from the percentages $100\ \hat{p}_{rs}$ with the appropriate weights, e.g.

$$\hat{p}_{r.} = \sum_{s} \hat{p}_{rs}n'_{rs}/n_{r.} ,$$

$$= \sum_{s} \hat{p}_{rs}n_{.s}/n_{..} .$$

We will refer to this procedure as computation from the expected cell percentages.

Computation of the expected marginal percentages from the expected cell percentages, if done by hand, is somewhat tedious, particularly in large multiway tables, since the expected percentages of the individual cells have first to be computed and their weighted means then taken. The question therefore arises whether the values of the fitted constants, which are given directly by the computation, can be used to provide values of expected marginal percentages.

In the analogous analysis of quantitative data the values of the fitted constants give direct estimates of the values the marginal means would assume if the cell frequencies were proportionate to the marginal frequencies. With exactly proportionate cell frequencies the values of fitted constants $m + a_r$ and $m + b_s$ are given directly by the two sets of marginal means. In the case of quantal data, however, retransformation of the values of the fitted constants $m + a_r$ and $m + b_s$ will give percentages which may differ widely from those obtained by computation from the expected cell percentages.

These differences are due to two causes. In the first place, since the fitted constants are in effect weighted means of the expected cell values of the transformed variates, the corresponding percentages will differ from the means, with the same weights, of the cell percentages.

In the second place the weights used in the fitting are the products of the cell frequencies and the weighting coefficients. The resultant fitted constants are therefore estimates of what the marginal means of the transformed variate would be if the weights were proportionate to the marginal sums of these weights instead of to the marginal frequencies. If the angular transformation, which has a constant weighting coefficient, is used, no differences will arise from this cause, but with other transformations it is frequently the major source of discrepancy.

At first sight it might appear that the best course would be to seek a value m' such that the quantities $m' + a_r$ when transformed give percentages whose weighted mean, using the marginal frequencies as weights, is equal to the observed overall percentage. This can be done without difficulty by successive approximation, and appears to be reasonably satisfactory with the angular transformation. When the percentages are small and the logit transformation is used, a much closer approximation to the marginal percentages computed from the expected cell percentages is obtained by the very simple procedure of transforming $m + a_r$ to percentages and multiplying all these percentages by a common factor, chosen so as to give the observed overall percentage, as is illustrated in the example below. This is to be expected since at the lower end of the percentage scale the use of the logit transformation implies that the cell percentages are representable by a product function of the form $u_r v_s$.

It may be noted here that even with the logit transformation the overall percentage computed from the expected cell percentages will differ from the observed overall percentage, owing to the change from actual to proportionate frequencies in the cells. The difference is not likely to be large, but for practical purposes it may be regarded as preferable to present marginal percentages whose weighted means are exactly equal to the observed overall percentage. For this purpose a proportional adjustment of all percentages (or their differences from 100 when all percentages are large) will be adequate.

EXAMPLE

Table 1 gives the percentages of cows affected by milk fever in given lactations, classified by lactation number and season of calving, and Table 2 the numbers of calvings on which these percentages are based. These results were obtained in the course of a survey of diseases of dairy cattle.

It is immediately apparent from the percentages that there is a much greater incidence of milk fever in the later calvings, and also a variation with season, January-April having the lowest incidence and

TABLE 1

PERCENTAGES OF COWS AFFECTED BY MILK FEVER

	Lactation					
	1–2	3	4	5	6+	Overall
Jan–Apr	0.42	1.45	3.15	5.57	6.07	2.67
May–July	0.17	3.08	7.37	9.43	10.94	4.17
Aug–Sept	0.66	4.89	9.40	10.93	13.98	4.25
Oct–Dec	0.35	2.93	6.07	9.61	12.19	3.50
Overall	0.41	2.75	5.58	8.06	9.38	3.46

August-September the highest. The August-September maximum is somewhat masked in the marginal percentages, however, owing to the greater proportions of these calvings in the earlier lactations.

Constants were fitted using the logit transformation with logs to base 2. The results shown in Table 3 were obtained. Inverse transformation of these logits gives percentages for seasons which are very much too high. This is mainly due to the low weighting coefficients associated with the low percentages of lactations 1 − 2.

The expected logits for the individual cells can be computed from the values of Table 3, and transformed to percentages. Thus the logit for the top left-hand cell is $-4.0121 - 2.3786 + 1.9874 = -4.4033$, and the corresponding expected percentage is 0.2229. The discrepancies between the weighted marginal means of these percentages, with weights equal to the original cell frequencies (Table 2), and the observed marginal percentages, are all less than 0.001.

TABLE 2

NUMBERS OF CALVINGS

	Lactation					
	1–2	3	4	5	6+	Total
Jan–Apr	3806	2137	1744	1184	2010	10881
May–July	2352	1006	706	488	841	5393
Aug–Sept	3169	1003	617	366	522	5677
Oct–Dec	5117	1740	1252	791	1042	9942
Total	14444	5886	4319	2829	4415	31893

TABLE 3

FITTED CONSTANTS (LOGITS TO BASE 2) AND CORRESPONDING PERCENTAGES

Lactation	$m + a_r$	%	Season	$m + b_s$	%
1–2	−4.0121	0.383	Jan–	−2.3786	3.566
3	−2.5643	2.779	May–	−1.9180	6.544
4	−2.0055	5.840	Aug–	−1.6682	9.009
5	−1.7082	8.564	Oct–	−1.9104	6.609
6+	−1.5678	10.220	—	—	—
m	−1.9874	5.980			

Table 4 gives the various estimates of the expected marginal percentages with proportionate weights. Line (1) gives the weighted means of the expected cell percentages, with weights equal to the marginal frequencies of Table 2. These give a small discrepancy in the overall percentage, and this is removed in line (2) by proportional adjustments. Line (3) is obtained by proportional adjustment of the percentages derived directly from the fitted constants (Table 3). The agreement

TABLE 4

MARGINAL PERCENTAGES COMPUTED BY VARIOUS METHODS

(1) From expected cell percentages, with proportionate weights
(2) Line (1) adjusted to observed overall percentage
(3) From fitted constants (adjusted)

Lactation

	1–2	3	4	5	6+	Overall
(1)	0.39	2.79	5.85	8.55	10.18	3.65
(2)	0.37	2.65	5.55	8.11	9.66	3.46
(3)	0.36	2.63	5.54	8.12	9.69	3.46

Season

	Jan	May	Aug	Oct	Overall
(1)	2.19	3.99	5.46	4.03	3.65
(2)	2.08	3.78	5.18	3.82	3.46
(3)	2.06	3.78	5.21	3.82	3.46

between lines (2) and (3) is very close. With the logit transformation and small percentages direct derivation from the fitted constants may therefore be regarded as quite satisfactory.

Comparison of these expected percentages with the observed percentages of Table 1 shows that the distortions in the observed marginal percentages due to disproportionate weights have been removed by the fitting.

The residual sum of squares given by the fitting is 17.57. This corresponds to a χ^2 with 12 *d.f.*, giving $.2 < P < .1$. The data are therefore reasonably represented by additive components in the logit scale.

MULTI-WAY TABLES

If only constants representing the main classifications are fitted the procedure of proportional marginal adjustment is exactly the same for three- or more-way tables as for two-way tables. If, however, constants representing certain sets of sub-classes (analogous to the interactions of a factorial experiment) are also fitted, the situation becomes more complex. Nevertheless if the expected values of the transformed variate are available only for the margins of the table, a procedure analogous to that given above for a two-way table will probably be quite satisfactory, but certain minor inconsistencies in the margins relating to the main classifications may be expected.

PROGRAMMING POINTS IN ELECTRONIC COMPUTATION

Any programme for the analysis of multiway tables of quantal data which follows the ordinary maximum likelihood procedure of successive approximation must embody provisions for computing the expected values, in terms of the transformed variate, of the individual cells of the table, since these values constitute the provisional values for the next approximation. It must also contain provision for forming the weighted marginal means, with disproportionate and probably also with proportionate weights. Consequently, in order to calculate the expected cell percentages all that is necessary, in the way of additions to the programme, is to re-calculate the expected values of the individual cells after the last approximation (this will probably be done in any case), transform these to percentages, and calculate the marginal means of these percentages with weights proportional to the marginal frequencies of the main classifications. If desired a proportional adjustment can be made to these percentages so as to give the observed overall percentage.

This procedure is likely to be just as simple, from the programming

point of view, as the alternative procedure of adjusting the marginal percentages proportionally and should therefore be adopted when writing a complete programme. The latter procedure is, however, of interest, since it makes it possible to deal expeditiously with results furnished by a programme for which no provision for inverse transformation has been made, or which only inversely transforms the expected marginal values of the transformed variate.

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SOME CLASSIFICATION PROBLEMS WITH MULTIVARIATE QUALITATIVE DATA[1]

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1. INTRODUCTION

Since 1935, when Fisher's discriminant function appeared in the literature, methods for classifying specimens into one of a set of universes, given a series of measurements made on each specimen, have been extensively developed for the case in which the measurements are continuous variates. This paper considers some aspects of the classification problem when the data are qualitative, each measurement taking only a finite (and usually small) number of distinct values, which we shall call *states*. Our interest in the problem arose from discussions about the possible use of discriminant analysis in medical diagnosis. Some diagnostic measurements, particularly those from laboratory tests, give results of the form: −, + (2 states); or −, doubtful, + (3 states); or (with a liquid), clear, milky, brownish, dark (4 states).

With qualitative data of this type an optimum rule for classification can be obtained as a particular case of the general rule (Rao, [1952], Anderson, [1958]). The rule is exceedingly simple to apply (Section 2). In practice, qualititative data are frequently ordered, as with −, doubtful, +. The classification rule discussed in this paper takes no explicit advantage of the ordering, as might be done, for instance, by assigning scores to the different states so as to produce quasi-continuous data. The best method of handling ordered qualitative data is a subject worth future investigation.

[1]This work was assisted by a contract between the Office of Naval Research, Navy Department, and the Department of Statistics, Harvard University by a Special Research Fellowship of the National Institutes of Health, and by a gift from the Lilly Research Laboratories to the Department of Biostatistics, University of Oregon Medical School. Reproduction in whole or in part is permitted for any purpose of the United States Government.

This paper seeks answers to three problems that arise in the use of the proposed rule.

(1) *The effect of the initial sample sizes on the performance of the proposed classification rule.*

In order to construct a rule, we must have preliminary data on some specimens known to be classified correctly, since the rule depends on the joint frequency distributions of the measurements within each universe. Standard classification theory assumes that these distributions are known exactly, although in practice it is sometimes difficult to obtain adequate samples from which to estimate them. The consequences of constructing a rule from preliminary samples of finite sizes are discussed in Sections 3, 4, and 5.

(2) *The relative discriminating power of qualitative and continuous variates.*

Classification is simpler with qualitative than with continuous measurements. For this reason, if a few of the available measurements are continuous while the rest are qualitative, we may be inclined to transform each continuous measurement into a qualitative one by partitioning its frequency distribution, provided that this does not result in too much loss of discriminating power. This consideration led us to investigate the questions: if a normally distributed variate is transformed into a qualitative one with s states, how much discriminating power is lost, and what are the best points of partition of the curve from the point of view of retaining maximum discriminating power (Sections 6 and 7)?

(3) *Use of classification experience for improvement of the rule.*

The optimum rule depends on the relative frequencies π_1 , π_2 , π_3 etc. with which specimens from the different universes present themselves for classification. The initial estimates of these frequencies, made from previous data or by judgement, may be biased. After a number of specimens have been classified by the rule, it is possible to re-estimate the frequencies π_u from the data for these specimens, so that the classification rule may be improved (Section 8).

2. AN OPTIMUM RULE FOR CLASSIFICATION

Ideally, the setting up of an optimum rule demands three different kinds of preliminary information. Firstly, we require the joint frequency distribution of the measurements in each universe under consideration. With continuous variates the most common assumption about these

distributions is that they are multivariate normal with the same dispersion matrix in each universe. With qualitative variates, suppose that the jth measurement takes s_j distinct states. When this measurement is made on a specimen, we learn into which state it falls. A series of qualitative measurements, e.g. one with 2 states, one with 3 states and one with 4 states, defines 24 cells or multivariate states. For any specimen, these three measurements tell us which of the 24 states the specimen occupies. Thus, in general, a set of k qualitative measurements classifies the specimen into one out of a number $S = s_1 s_2 \cdots s_k$ multivariate states. Consequently the joint frequency distribution of the measurements is completely specified for the uth universe if we know the probabilities p_{ui} that the specimen falls into the ith multivariate state where, for each u,

$$\sum_{i=1}^{S} p_{ui} = 1.$$

Secondly, practical use of a classification rule is likely to result in some mistakes in classification. In some applications certain types of mistakes are more serious than others. If the relative costs of different kinds of mistakes can be estimated, the rule should take them into account. Let c_{vu} be the cost incurred when a specimen which actually belongs to universe V is classified as belonging to universe U.

Thirdly, when the rule is put into use, the specimens to be classified may not come with equal frequency from the universes. For instance, in a diagnostic screening test, most of the subjects who present themselves may be free from the disease in question. Let π_u denote the relative frequency with which specimens come from the uth universe, where

$$\sum_{u} \pi_u = 1.$$

As might be expected, the optimum rule depends on these frequencies.

With this background we now construct an optimum rule. For a specimen which falls into the ith multivariate state, we select the universe to which it is to be assigned by minimizing the expected cost of mistakes in classification. Suppose that the specimen is assigned to the uth universe. For specimens that actually come from this universe, no mistake is made. Specimens from the vth universe will present themselves with relative frequency π_v , and will fall into the ith state with relative frequency $\pi_v p_{vi}$. The expected cost of misclassifying these specimens into the uth universe is therefore $\pi_v p_{vi} c_{vu}$. Hence the total expected cost of mistakes in classification is

$$\sum_{v \neq u} \pi_v p_{vi} c_{vu} .$$

To apply the optimum rule we compute this quantity for every u and assign specimens to the universe for which the quantity is a minimum.

There are several particular cases of the rule. If $c_{vu} = c_v$, i.e. the cost of misclassifying depends only on the universe from which the specimen comes and not on that into which it is misclassified, the total expected cost over all m universes is

$$\sum_{v \neq u} \pi_v p_{vi} c_v = \sum_{v=1}^{m} \pi_v p_{vi} c_v - \pi_u p_{ui} c_u .$$

Since the first term on the right does not depend on u, specimens falling into the ith state are assigned to the universe for which the triple product $\pi_u p_{ui} c_u$ is greatest.

If the relative costs c_u are taken as equal, the rule minimizes the expected frequency of mistakes in classification. If, further, the relative frequencies π_u are also equal, any specimen found in the ith state is assigned to the universe u for which the conditional probability p_{ui} is greatest.

For a numerical example we are indebted to Dr. Leslie Kish. The data come from a large study of voting behavior conducted by the Survey Research Center, University of Michigan. (Stokes *et. al.* [1958]). By open-end questionnaires taken during the 1952 and 1956 elections, voters were rated as Democrats (D), Independents (I) or Republicans (R) and also as Unfavorable (U), Neutral (N) or Strongly Favorable (F) to Eisenhower's personality. These are the two predictor measurements, each with 3 states, making 9 bivariate states. The voters were also asked whether they voted for Stevenson or Eisenhower, these being the two universes. The sample sizes were 1003 and 1439.

For illustrative purposes we have set up a rule classifying the subjects as Stevenson or Eisenhower voters by means of the predictor variates. The results of the classification are then compared with the actual voting behavior.

Table 1 shows the relative frequencies p_{1i} and p_{2i} of the ith state for Stevenson and Eisenhower voters respectively. We assumed that $c_1 = c_2$ and that $\pi_1 = \pi_2 = \frac{1}{2}$. The resulting classification rule is given on the right in Table 1. Persons falling into the states DU, DN, DF and IU are classified by the rule as Stevenson voters, since in these states $p_{1i} > p_{2i}$.

The estimated probabilities of misclassification are easily obtained. Any Eisenhower voter is misclassified if he falls into the states DU, DN,

DF or *IU*. Hence the frequency of misclassification for Eisenhower voters is

$$.033 + .079 + .090 + .017 = .219.$$

The figure for Stevenson voters is 0.133 and the average is 0.176.

As with continuous measurements, it is possible to examine whether a measurement contributes to the classification to a worthwhile extent. If political affiliation alone (D, I, R) is recorded, the probabilities in the three states are given in the lower part of Table 1, being obtained of course by addition from the upper part of the table. The probabilities of misclassification are now 0.201 for Stevenson voters and 0.202 for Eisenhower voters. Thus the addition of the attitude measurement reduces the average number of mistakes by about 13 percent.

The use of qualitative variates in attempting to date certain of the

TABLE 1

ILLUSTRATION OF THE CLASSIFICATION RULE FOR TWO MEASUREMENTS

State (i)	p_{i1} Stevenson	p_{i2} Eisenhower	Resulting classification rule
DU	.347	.033	S
DN	.359	.079	S
DF	.094	.090	S
IU	.068	.017	S
IN	.078	.107	E
IF	.026	.154	E
RU	.002	.017	E
RN	.023	.176	E
RF	.004	.327	E
	1.001	1.000	

PROBABILITIES USING POLITICAL AFFILIATION ALONE

State	Stevenson	Eisenhower	Classification
D	.800	.202	S
I	.172	.278	E
R	.029	.520	E

works of Plato (i.e. to arrange a number of universes in a time sequence) has been discussed by Cox and Brandwood [1959].

In the rest of this paper discussion will be confined unless otherwise mentioned to the case of two universes, with $c_1 = c_2 = 1$ and $\pi_1 = \pi_2 = \frac{1}{2}$.

3. EFFECTS OF THE FINITE SIZES OF THE INITIAL SAMPLES

The initial sample from each universe serves two purposes. It is used to set up the classification rule and to estimate the probabilities of misclassification for specimens from the two universes, so that we can decide whether the classification is accurate enough to be satisfactory.

Some notation will be needed. To avoid double subscripts, let U, U' denote the two universes, and p_i , p_i' the true probabilities that a specimen will fall into the ith multivariate state. Independent samples of sizes n, n' are drawn from the universes. The numbers of specimens falling into the ith state are r_i , r_i' , and the corresponding estimated probabilities are $\hat{p}_i = r_i/n$, $\hat{p}_i' = r_i'/n'$. Since the true p_i , p_i' are unknown, the actual classification rule places a specimen in U if $\hat{p}_i > \hat{p}_i'$, in U' if $\hat{p}_i < \hat{p}_i'$. If $\hat{p}_i = \hat{p}_i'$, the decision is made by tossing a fair coin.

For given sample sizes n, n' the values of $\hat{p}_i$ and $\hat{p}_i'$ will vary from sample to sample. Thus the actual classification rule and its performance may change from sample to sample. In describing the consequences of finite sample sizes, we usually present the average results over all initial samples of given sizes n, n'.

The principal consequences of the finite sample sizes are as follows.

1. The probability of misclassification as estimated from the samples is, of course, subject to a sampling error that in moderately large samples may be shown to be approximately of the binomial type.

2. On the average, taken over all pairs of samples from a given pair of universes, the actual probability of misclassification is *greater* than the theoretical optimum: i.e. than the probability that would hold if the true p_i , p_i' were used to construct the classification rule.

3. The average estimated probability of misclassification is *less* than the theoretical optimum probability. From 2, it is also less than the average actual probability.

In other words, finite sample sizes involve two types of penalty. Owing to sampling errors in the $\hat{p}_i$, $\hat{p}_i'$, the rule obtained may not be the theoretical optimum, and the probability of misclassification is underestimated from the sample data.

These results may be illustrated, in exaggerated form, by considering samples of size $n = 1$ from universes having two states with the following true probabilities of falling into the states. With the

optimum rule the probability of misclassification is 0.1 for specimens from U, 0.05 for specimens from U', the average being 0.075.

State	U	U'	Optimum classification
1	0.9	0.05	U
2	0.1	0.95	U'

With $n = 1$, only four types of sample result are possible. Table 2 shows for each type the classification rule that would be set up, the estimated probability of misclassification, and the actual probability that would pertain if that rule were used. A ? means that classification is a toss-up.

To explain the entries in Table 2, consider the last type of result. The wrong classification is made in both states. Nevertheless, if we

TABLE 2

THE CLASSIFICATION RULE FOR SAMPLES OF SIZE 1

Sample result				Frequency of occurrence	Probability of misclassification	
					Estimated	Actual
State	U	U'	Rule			
1	1	0	U	(0.9)(0.95)		
2	0	1	U'	=0.855	0.0	0.075
1	1	1	?	(0.9)(0.05)		
2	0	0	?	= 0.045	0.5	0.500
1	0	0	?	(0.1)(0.95)		
2	1	1	?	= 0.095	0.5	0.500
1	0	1	U'	(0.1)(0.05)		
2	1	0	U	= 0.005	0.0	0.925
				Average	0.07	0.13875

believe the samples, we estimate a zero probability of misclassification. The actual probabilities are 0.9 for U and 0.95 for U', giving an average of 0.925.

The overall average actual probability of misclassification is 0.13875 as compared with a theoretical optimum of 0.075 and an average estimated value of 0.07.

The fact that the average actual probability exceeds the theoretical optimum arises, of course, because when $p_i > p_i'$, there will be some pairs of samples in which $\hat{p}_i \leqq \hat{p}_i'$. Whenever this occurs, the actual rule for this state is not as good as the optimum.

The fact that the average estimated probability lies below the theoretical optimum probability may be shown as follows. If $p_i > p_i'$, the contribution of this state to the overall theoretical probability of misclassification is $\frac{1}{2}p_i'$. Since r_i'/n' is an unbiased estimate of p_i', the contribution may be written $\frac{1}{2}E(r_i'/n')$, where E denotes a mean value. The estimated contribution, on the other hand, is $\frac{1}{2}$ the average of the *smaller* of r_i/n, r_i'/n', which will always be less than $\frac{1}{2}E(r_i'/n')$.

The bias in the estimated probability and the inferiority of the actual to the optimum rule are due primarily to states in which p_i differs little from p_i'. These difficulties can be largely avoided by withholding a decision, i.e. making no classification, in such states. For instance, suppose that preliminary samples of size 64 give the following results for a variate with four states.

	No. of specimens		
State	U	U'	
1	51	1	
2	8	5	
3	3	5	
4	2	53	
	64	64	

States 1 and 4 provide good discrimination, but in states 2 and 3 the estimated probabilities of a correct classification are only about 0.6. Consider a recommended rule to withhold judgement when a specimen occurs in state 2 or 3. From the samples, we have an unbiased estimate 21/128, or 16 percent, of the proportion of specimens for which the rule makes no classification. This estimate is binomial, with standard error $\sqrt{(0.16)(0.84)/128}$. When a decision is made, the probability

of misclassification is estimated as 3/107, or about 3 percent. This estimate will be almost exactly a binomial variate, with negligible bias.

If, on the contrary, a decision is made in all states, we would like to obtain from the initial samples a reasonably unbiased estimate of the probability of misclassification for the actual rule developed from the samples. An estimate of the difference between the actual and the theoretical optimum probability of misclassification is also of interest, particularly when it is not too costly to increase the size of the initial samples. These topics are discussed in Sections 4 and 5.

4. ESTIMATION OF THE THEORETICAL OPTIMUM PROBABILITY

As shown in Section 3, the sample probability of misclassification is a negatively biased estimate of the theoretical optimum probability. For a given value of $(p_i + p_i')$, it appears intuitively that the underestimation will be greatest when $p_i = p_i'$. In this case the bias in the ith state is in absolute value,

$$\tfrac{1}{2}p_i - \{\tfrac{1}{2}E \min. (\hat{p}_i , \hat{p}_i')\}$$

where $\hat{p}_i$, $\hat{p}_i'$ are independent binomial estimates of p_i . An algebraic expression for this quantity as a function of p_i , can be developed from the binomial distribution, but is unwieldy unless n, n' are small. An approximation to the bias may be obtained by regarding $\hat{p}_i$, $\hat{p}_i'$ as normally distributed. Since the average value of the smaller of two normal deviates is known to be -0.56, the bias in the estimate of p_i when both samples are of size n is approximately

$$-0.56 \sqrt{p_i q_i / n}.$$

With $p_i = p_i' = 0.05$, $n = 50$, for instance, this estimate gives -0.0173 as against the correct value of -0.0170.

Since this problem will occur mainly in states with low frequencies (unless the classification rule is poor), a relatively crude sample adjustment for bias should be adequate for estimating the overall theoretical optimum probability of misclassification. One suggestion is to use $(\hat{p}_i + \hat{p}_i')/4$ instead of one-half the smaller of $\hat{p}_i$, $\hat{p}_i'$ when estimating the probability of misclassification, this adjustment being made in states in which $\hat{p}_i$, $\hat{p}_i'$ do not differ significantly at, say, the 20 percent level of significance. In the numerical example above, the adjustment is made in states 2 and 3. It amounts to estimating the theoretical optimum probability as

$$\frac{1 + 6.5 + 4 + 2}{128} = \frac{13.5}{128} = 10.5\%$$

as compared with the unadjusted estimate of 11/128 or 8.6 percent.

Examination of individual cases indicates that this adjustment removes most of the bias in states in which $p_i = p_i'$. When $p_i \neq p_i'$ the adjustment tends to over-correct, and on the whole is likely to be conservative.

5. THE AVERAGE INCREASE IN THE ACTUAL PROBABILITY OF MISCLASSIFICATION

The average increase in the actual over the theoretical probability of misclassification may be expressed as a function of the p_i, p_i' and the sample sizes n (assumed equal). In the ith state, if $p_i > p_i'$, the optimum rule gives no misclassification for specimens from U, but misclassifies the proportion p_i' of specimens from U' that are in this state. The average frequency of misclassification is therefore $\frac{1}{2}p_i'$. With the samples, there is no increase in this frequency provided that $r_i > r_i'$. If $r_i = r_i'$, we toss a coin. This gives an increase in frequency of

$$\tfrac{1}{4}(p_i + p_i') - \tfrac{1}{2}p_i' = \tfrac{1}{4}(p_i - p_i').$$

If $r_i < r_i'$, we make the wrong decision, with an increase in frequency of mistakes of

$$\tfrac{1}{2}p_i - \tfrac{1}{2}p_i' = \tfrac{1}{2}(p_i - p_i').$$

Hence, over all states for which $p_i > p_i'$, the total expected increase in frequency of misclassification may be written

$$\tfrac{1}{2} \sum (p_i - p_i')\{\Pr.\ (r_i < r_i') + \tfrac{1}{2} \Pr.\ (r_i = r_i')\}, \tag{5.1}$$

with an analogous expression for the states in which $p_i < p_i'$.

The probability inside the curly brackets may be obtained from tables of the binomial distribution. The normal approximation to this quantity is surprisingly good, even for moderate samples and small p_i, p_i'. With this approximation, the estimate is the probability that a normal deviate is less than

$$-\frac{\sqrt{n}\,|\,p_i - p_i'\,|}{\sqrt{p_iq_i + p_i'q_i'}} \tag{5.2}$$

No correction for continuity is applied, because of the presence of the term $\frac{1}{2}Pr.\ (r_i = r_i')$ in the exact expression. As an example of the accuracy, with $p_i = 0.03$, $p_i' = 0.01$, $n = 100$, the normal approximation gives 0.1555 as compared with the exact value 0.1567.

Use of the normal approximation is illustrated in Table 3. From the $\hat{p}_i$, $\hat{p}_i'$ for each state the normal deviate is computed from (5.2) and the probability is read from the normal tables. The difference

TABLE 3

ESTIMATION OF ACTUAL MINUS OPTIMUM PROBABILITY OF MISCLASSIFICATION

State	No. of specimens U	U'	N.D.	Probability	$\lvert \hat{p}_i - \hat{p}'_i \rvert$
1	51	1	Large	0.0	—
2	8	5	−0.880	0.189	0.0469
3	3	5	−0.732	0.232	0.0312
4	2	53	Large	0.0	—
Total	64	64			

between the average actual and the theoretical probability of misclassification is estimated as

$$\tfrac{1}{2}\{(0.189)(0.0469) + (0.232)(0.0312)\} = 0.0080 = 0.8\%.$$

At the end of Section 4 the theoretical probability of misclassification was estimated as 10.5 percent. Adding 0.8 percent, we estimate the expected actual probability as 11.3 percent.

In order to obtain a general impression of the effect of sample size, some study was made of expression (5.1) for the average increase of the actual over the theoretical optimum probability, as a function of p_i , p'_i , n, and S, the number of states. The difficulty in studying this function lies in the substantial number of parameters involved when the states are numerous. A preliminary search was made for a smaller number of parameters which might dominate the performance of the function. It became evident that the function depends on the overall optimum probabilities of misclassification, i.e. on the quantities

$$P = \sum_{p_i < p'_i} p_i \,, \qquad P' = \sum_{p'_i < p_i} p'_i \,.$$

As P, P' diminish, i.e. as the optimum rule becomes better, the average increase also diminishes, i.e. the actual rule is less likely to differ from the theoretical optimum. Even with the quantities P, P', n and S fixed, the average increase may vary from almost zero up to a maximum, depending on the way in which p_i , p'_i distribute themselves among the states. We decided to tabulate the maximum increase for given P, P', n and S, although aware that this might produce an unduly pessimistic view of the effect of finite sample size. The worst possible distributions of the p_i , p'_i were found by trial and error. In most situations, though not in all, the worst case occurs when the probability

P' is distributed equally among all but one of the states for which $p_i > p_i'$. As an example, for 8 states, with $P = P' = 0.1$, the worst distribution in the first four states is as follows.

p_i	p_i'
.69	.0
.07	.0333
.07	.0333
.07	.0333

Table 4 shows the maximum average increases for $n = 50$ 00 $S = 4, 8, 16, 32$; $P = P' = 0.05$. 0.1, 0.2, 0.3, 0.4.

TABLE 4

MAXIMUM AVERAGE INCREASE IN PROBABILITY OF MISCLASSIFICATION

Opt. Prob. $P = P'$	$n = 50$ Number of states 4	8	16	32	$n = 100$ Number of states 4	8	16	32
0.05	.009	.018	.032	.059	.006	.011	.020	03-
0.1	011	.022	.039	.067	.008	015	.025	041
0.2	014	.027	.049	.082	.010	020	.033	.052
0.3	.016	.034	.057	.098	.011	.023	.038	.062
0.4	.025	.037	.061	.071	.012	.026	.041	.061

As mentioned previously, the average increase is smallest when P, P' are small. It becomes larger as the number of states increases, being somewhat less than doubled for each doubling of the number of states. The average increases for $n = 100$ are roughly $1/\sqrt{2}$ times those for $n = 50$. Some irregularities in the table will be noticed for $P = 0.4$. The explanation is that the actual rule always gives at least 50 percent correct classifications. This imposes an upper limit to the maximum average increase for $P = 0.4$.

It is difficult to give general recommendations from this analysis. The following comments may be appropriate.

1. Preliminary samples of around 50 specimens from each universe should give a good indication of those multivariate states in which the classification will be accurate, and of those in which it will be dubious.

2. If a classification is to be made for all multivariate states, the estimated probabilities of misclassification should be increased by the two adjustments for bias.

3. If the number of multivariate states does not exceed 8, Table 4 suggests that samples of size 50 should make the actual rule satisfactorily close to the optimum in most situations. With 8 states and $n = 50$, the actual probabilities in the worst cases are 6.8, 12.2, 22.7 and 33.4 percent, for theoretical optimum probabilities of 5, 10, 20 and 30 percent, respectively. For larger numbers of states, substantially greater samples are indicated.

6. THE EFFECT OF REPLACING A NORMAL VARIATE BY A QUALITATIVE VARIATE

When some variates are continuous and some qualitative, Rao's general rule for classification still applies. However, it presents difficulties in application, as Linhart [1959] has pointed out, since a different continuous discriminant is required for each multivariate state defined by the qualitative variates.

In this section the loss of discriminating power when normally distributed variates are partitioned into qualitative variates is examined. It is assumed that the variates are independent. This assumption is unrealistic for applications, but we have not been able to reach general results with correlated variates. With independent variates, simple asymptotic results can be obtained when the number of variates becomes large, and can be checked against the exact results for a small number of variates.

Let the vth continuous variate be denoted by y_v, $(v = 1, \cdots, k)$, and the two universes by A and B. The variate y_v is normal, with s.d. unity in each universe, and with mean 0 in A and δ_v in B, the quantity δ_v being "the distance apart" of the two populations. The larger δ_v is, the better y_v is for classification.

Given k independent variates, it is easy to show that the best continuous discriminator, when divided so that its standard deviation is 1, is the quantity

$$R_v = \sum \delta_v y_v / \sqrt{\sum \delta_v^2} . \tag{6.1}$$

For this discriminator the distance between the two populations is $\sqrt{\sum \delta_v^2}$. As k becomes large with all $\delta_v > 0$, the distance becomes so great that classification is almost perfect. In order to discuss the situation in which some mistakes in classification are made, we assume that as k becomes large the δ_v tend to zero in such a way that $\sqrt{\sum \delta_v^2}$ remains finite.

The continuous classification rule assigns a specimen to B if $R_e \geq \frac{1}{2}\sqrt{\sum \delta_v^2}$. Since R_e is normally distributed, the probability of misclassification, which is the same for both universes, is the probability that a normal deviate is greater than $\frac{1}{2}\sqrt{\sum \delta_v^2}$.

Let each continuous variate be partitioned into a qualitative variate with six states. Results for fewer than six states are derived as particular cases of the result for six states. For the vth variate, let Pr. $(j_v \mid A)$, Pr. $(j_v \mid B)$ be the probabilities that a specimen from A and B respectively falls into the j_vth state. The 6^k multivariate states into which the specimen can fall may be specified by recording the states j_1, j_2, $\cdots$, j_k for the individual variates. Since the variates are independent, the probabilities that a specimen falls into a given multivariate state are

$$\prod_{v=1}^{k} \text{Pr. } (j_v \mid A) \quad \text{and} \quad \prod_{v=1}^{k} \text{Pr. } (j_v \mid B).$$

Consequently the optimum discrete rule places a specimen in A if

$$\prod_{v=1}^{k} \text{Pr. } (j_v \mid A) > \prod_{v=1}^{k} \text{Pr. } (j_v \mid B),$$

i.e. if

$$\sum_{v=1}^{k} \{\log \text{Pr. } (j_v \mid A) - \log \text{Pr. } (j_v \mid B)\} > 0. \tag{6.2}$$

This may be written

$$\sum x_v > 0 \tag{6.2}'$$

where

$$x_v = \log \text{Pr. } (j_v \mid A) - \log \text{Pr. } (j_v \mid B).$$

The quantity $\sum x_v$ is a discrete random variable with 6^k possible values, since its value depends on the multivariate state into which the specimen falls. It will be shown that as k becomes large, this quantity tends to be normally distributed.

The way in which an individual variate is partitioned is shown in Figure 1. The six states are labeled, for mnemonic reasons, A, a, α, β, b, B: they might be called "strongly, moderately, slightly favorable to A", etc. The partition involves two disposable numbers u_1, u_2, which determine the sizes of the regions α, β and a, b. (Four numbers might be used, but symmetry suggests that two will give the best partition.) Strictly, the numbers should be denoted by u_{1v}, u_{2v}, since it may be profitable to vary them with v, but for simplicity the subscript v will be omitted from u_1, u_2 and δ at present.

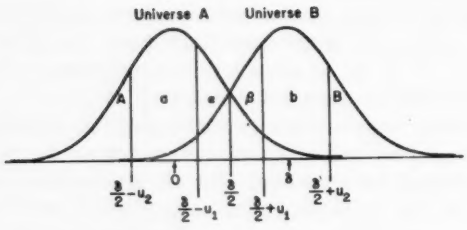

FIGURE 1

PARTITION OF A NORMAL VARIATE INTO SIX STATES

For an individual variate v Table 5 shows the notation used for the probabilities of falling into the respective states.

The probabilities p_i are integrals over the parts of the normal curve indicated in Figure 1. Note that the Pr. ($| B$) values are the same as the Pr. ($| A$) values in reverse order.

TABLE 5

PROBABILITIES THAT A VARIATE WILL FALL INTO THE 6 STATES

	State					
	A	a	α	β	b	B
Pr. ($\mid A$)	p_1	p_2	p_3	p_4	p_5	p_6
Pr. ($\mid B$)	p_6	p_5	p_4	p_3	p_2	p_1
x	w_1	w_2	w_3	$-w_3$	$-w_2$	$-w_1$

The last line of Table 5 shows the six possible values taken by the random variable

$$x = \log \text{Pr.} (\mid A) - \log \text{Pr.} (\mid B)$$

where

$$w_1 = \log (p_1/p_6), \quad w_2 = \log (p_2/p_5), \quad w_3 = \log (p_3/p_4).$$

It follows from Table 5 that

$$E(x \mid A) = w_1(p_1 - p_6) + w_2(p_2 - p_5) + w_3(p_3 - p_4)$$

while $E(x \mid B)$ has the same value with sign reversed. The variance has the same value for both universes, namely

$$V(x) = w_1^2(p_1 + p_6) + w_2^2(p_2 + p_5) + w_3^2(p_3 + p_4) - [E(x \mid A)]^2.$$

Reverting to inequality (6.2)′, its left side is the sum of a large number of independent variables x, and hence tends to become normally distributed as k becomes large.

It remains to obtain the values of $E(x \mid A)$ and $V(x)$ when δ tends to zero. The leading terms in the expressions for the p_i and the w_i are found to be as follows.

Let

$$I_1 = \int_{u_1}^{\infty} z(t)\,dt, \qquad I_2 = \int_{u_2}^{\infty} z(t)\,dt$$

where $z(t)$ is the normal curve, and let z_0 , z_1 , z_2 be the ordinates of this curve at 0, u_1 , u_2 , respectively. Then, from Figure 1,

$$p_1 = \int_{-\infty}^{\frac{1}{2}\delta - u_2} z(t)\,dt \doteq I_2 + \tfrac{1}{2}\delta z_2 ,$$

$$p_2 = \int_{\frac{1}{2}\delta - u_2}^{\frac{1}{2}\delta - u_1} z(t)\,dt \doteq I_1 - I_2 + \tfrac{1}{2}\delta(z_1 - z_2).$$

Similarly,

$$p_3 \doteq \tfrac{1}{2} - I_1 + \tfrac{1}{2}\delta(z_0 - z_1), \qquad p_4 \doteq \tfrac{1}{2} - I_1 - \tfrac{1}{2}\delta(z_0 - z_1),$$

$$p_5 \doteq I_1 - I_2 - \tfrac{1}{2}\delta(z_1 - z_2), \qquad p_6 \doteq I_2 - \tfrac{1}{2}\delta z_2 ,$$

$$w_1 \doteq \frac{\delta z_2}{I_2}, \qquad w_2 \doteq \frac{\delta(z_1 - z_2)}{I_1 - I_2}, \qquad w_3 \doteq \frac{\delta(z_0 - z_1)}{\frac{1}{2} - I_1}.$$

Substituting these values in $E(x \mid A)$ and $V(x)$, retaining only the terms of order δ^2, we find

$$E(x \mid A) = \delta^2\left\{\frac{z_2^2}{I_2} + \frac{(z_1 - z_2)^2}{I_1 - I_2} + \frac{(z_0 - z_1)^2}{\frac{1}{2} - I_1}\right\}. \tag{6.3}$$

$$V(x) = 2E(x \mid A) = 2\,\delta^2 f(u_1 , u_2), \tag{6.4}$$

writing $f(u_1 , u_2)$ for the expression in brackets in (6.3).

We now reintroduce the subscript v in order to sum over the k variates. From inequality (6.2)′ the probability of misclassifying a specimen from A is the probability that the random variable $\sum (x_v \mid A)$ is negative. From (6.3) and (6.4) this variable is approximately normally distributed with

$$\text{Mean} = \sum_{v=1}^{k} \delta_v^2 f(u_{1v} , u_{2v}) : \quad \text{Variance} = 2 \sum_{v=1}^{k} \delta_v^2 f(u_{1v} , u_{2v}).$$

Hence the probability of misclassifying an A is approximately the probability that a normal deviate exceeds

$$\sqrt{\sum \delta_v^2 f(u_{1v} , u_{2v})/2}. \tag{6.5}$$

In order to minimize the probability we must maximize (6.5). Since $f(u_{1s}, u_{2s})$ does not depend on δ_s, expression (6.5) shows that the maximum is attained by substituting the *same* values of u_{1s}, u_{2s} in every term, i.e. the values which maximize $f(u_1, u_2)$. This reduces (6.5) to

$$\sqrt{\text{max. } f(u_1, u_2)}\ \sqrt{\sum \delta_s^2/2}. \tag{6.6}$$

With the untransformed normal variate it was shown earlier that the best rule gives a probability of misclassification equal to the probability that a normal deviate exceeds $\frac{1}{2}\sqrt{\sum \delta_s^2}$. Comparing this result with (6.6), the relative discriminating power of the best qualitative to the best continuous rule is

$$2 \text{ max. } f(u_1, u_2) = 2 \text{ max. } \left\{\frac{z_2^2}{I_2} + \frac{(z_1 - z_2)^2}{I_1 - I_2} + \frac{(z_0 - z_1)^2}{\frac{1}{2} - I_1}\right\}. \tag{6.7}$$

This result holds in the sense that if a randomly chosen fraction 2 max. $f(u_1, u_2)$ of the original normal variates is retained, discarding the rest, the best continuous rule becomes equivalent to the best qualitative rule based on all the variates.

The result for five states is obtained by ignoring the distinction between the states α and β, calling the combined state D (doubtful). The effect is that the last term on the right of (6.7) disappears. For four states we let $u_1 = 0$, the states becoming A, a, b, B. For three states, the states a and b are combined into a D region. Finally, for two states we put $u_2 = 0$.

The form of the expression $2f(u_1, u_2)$, the values of u_1, u_2 giving the best partition of the normal curve, and the relative discriminating power of the qualitative variates appear in Table 7 for 2, 3, 4, 5 and 6 states.

Since the maxima of $f(u_1, u_2)$ are flat, the best values of u_1 and u_2 are given only to one decimal. For two states, the relative power is $2/\pi$, which will be familiar as the asymptotic power of the sign test. Use of five or six states retains over 90 percent of the power.

The function $2f(u_1, u_2)$ has already appeared in two other problems involving the replacement of normal curve methods by less efficient methods. Ogawa [1951] obtained this function as the efficiency of estimation of the population mean from suitably chosen order statistics in large samples. D. R. Cox [1957] found the same expression for the relative amount of information retained by grouping the normal curve when the group boundaries are chosen to minimize the quantity $E\{x - \mu(x)\}^2/\sigma^2$, where $\mu(x)$ is the mean of the group to which x is assigned. So far as we can see, the three problems are mathematically

TABLE 7

THE ASYMPTOTIC RELATIVE DISCRIMINATING POWER OF QUALITATIVE TO CONTINUOUS NORMAL VARIATES

No. of states	$2J(u_1, u_2)$	Best values of u_1	Best values of u_2	Relative power
2	$2/\pi$	—	—	0.636
3	$2z_2^2/I_2$	—	0.6	0.810
4	$2\left\{\frac{z_2^2}{I_2} + \frac{(z_0 - z_2)^2}{\frac{1}{2} - I_2}\right\}$	—	1.0	0.882
5	$2\left\{\frac{z_2^2}{I_2} + \frac{(z_1 - z_2)^2}{I_1 - I_2}\right\}$	0.4	1.2	0.920
6	$2\left\{\frac{z_2^2}{I_2} + \frac{(z_1 - z_2)^2}{I_1 - I_2} + \frac{(z_0 - z_1)^2}{\frac{1}{2} - I_1}\right\}$	0.7	1.4	0.942

different, and the identity of results, as Cox has pointed out, seems to depend on particular properties of the normal curve.

7. COMPARISONS FOR SMALL NUMBERS OF VARIATES

As a check on the utility of the asymptotic results for practical situations, the best points of partition and the resulting probabilities of misclassification were computed directly for small numbers of variates. For simplicity the distance apart δ was assumed to be the same for all variates.

Having calculated the probability of misclassification for a given δ and number of variates k, we can compute the number k' of continuous normal variates that are needed to give the same probability of misclassification. For these values of δ and k, the ratio k'/k gives the relative discriminating power of the qualitative to the continuous normal variates. Unlike the asymptotic case, this ratio is of course dependent on the values of δ and k. For fixed k, however, the ratio turns out to be almost constant to two decimal places over the range of probabilities of misclassification that are of practical interest.

In the top half of Table 8, the relative discriminatory power with two variates is compared with the asymptotic power from Table 7

TABLE 8

RELATIVE DISCRIMINATING POWER OF QUALITATIVE TO CONTINUOUS NORMAL VARIATES FOR SMALL NUMBERS OF VARIATES

2 states		3 states		4 states		5 states	
$k = 2$	$k = \infty$	$k = 2$	$k = \infty$	$k = 2$	$k = \infty$	$k = 2$	$k = \infty$
.50	.64	.74	.81	.84	.88	.89	.92

2 states							3 states				
k							k				
2	3	4	5	6	7	∞	2	3	4	5	∞
.50	.74	.56	.70	.58	.68	.64	.74	.76	.77	.78	.81

for 2, 3, 4 and 5 states. The "small-sample" powers are all lower than the asymptotic values.

The lower half of Table 8 shows the results with two states and from 2 to 7 variates. The results have one curious feature. With an odd number of variates the relative powers are higher than the asymptotic values. The explanation may be that none of the decisions requires the toss of a coin when the number of variates is odd. In line with this result is the fact that with two states and only one variate ($k = 1$) the classification rule is the same as that obtained from the original normal variate, so that the relative power is unity. With 3 states (Table 8) this peculiarity does not appear, the relative powers increasing steadily with k towards the asymptotic value.

The optimum values of u_1 and u_2 for small numbers of variates were consistently close to the asymptotic optima. This result held throughout a wide range of values of $\delta \sqrt{k}$ from 0.5 (corresponding to a probability of misclassification of over 40 percent) to 4. Since, moreover, the optima are flat, the asymptotic values of u_1 and u_2 may be used safely with only two variates.

A few comparisons have been made between the qualitative and continuous discriminators for the case of two correlated variates of equal discriminating power. Suppose that the continuous scales are arranged so that the variates have standard deviations unity, with means zero in population A and δ in population B. If they are positively correlated, as appears to be the more common situation in applications, results obtained for 2 and 3 states indicate that the qualitative discriminator has higher relative power than when the variates are independent. The reverse seems to hold with negative correlation. Consequently our results for independent variates cannot be assumed

to be valid for correlated variates. More investigation is needed.

In order to transform a continuous into a qualitative variate in an application we compute the means $\bar{y}_A$, $\bar{y}_B$ of the continuous variate in the initial samples from the two universes and the pooled within-universes standard deviation s. Let $\bar{y} = (\bar{y}_A + \bar{y}_B)/2$. With, for instance, five states the best asymptotic values of u_1 , u_2 are $u_1 = 0.4$, $u_2 = 1.2$. The states are constructed as follows.

Value of y	State
less than $\bar{y} - 1.2s$	A
from $\bar{y} - 1.2s$ to $\bar{y} - 0.4s$	a
from $\bar{y} - 0.4s$ to $\bar{y} + 0.4s$	D
from $\bar{y} + 0.4s$ to $\bar{y} + 1.2s$	b
greater than $\bar{y} + 1.2s$	B

8. ESTIMATION OF THE RELATIVE FREQUENCY WITH WHICH SPECIMENS COME FROM THE TWO UNIVERSES

If specimens present themselves with unequal frequencies π, π' from the two universes, the optimum rule is to assign a specimen to U if $\pi p_i > \pi' p'_i$. This rule requires an initial estimate or guess about the value of π. With qualitative variates the accuracy of this figure will often be not critical, because the same optimum rule holds over a range of values of π, although the range becomes shorter as the number of states increases. Table 9 gives an illustration for 4 states. The horizontal line marks the boundary of the best decision region.

TABLE 9

THE OPTIMUM RULE FOR DIFFERENT VALUES OF π

	Range of π .011 − .4		Range of π .4 − .64		Range of π .64 − .99	
State	p_i	p'_i	p_i	p'_i	p_i	p'_i
1	.92	.01	.92	.01	.92	.01
2	.06	.04	.06	.04	.06	.04
3	.04	.07	.04	.07	.04	.07
4	.00	.88	.00	.88	.00	.88

If we guessed $\pi = \pi' = 0.5$, we would use the middle classification rule in Table 9. This remains the best rule so long as π lies between 0.4 and 0.64. Even with π outside these limits, this rule may be close to the best. For instance, if π is 0.7, the average frequency of misclassification using our rule is (.7)(.04) + (.3)(.05), or .043, as against (.3)(.12), or .036 with the optimum rule. With $\pi = 0.8$ the corresponding figures are .042 and .024, a more serious difference.

When m specimens have been classified, the data give the numbers of specimens r_i found in each state, where $\sum r_i = m$. If the p_i , p_i' are known, the r_i follow a multinomial distribution with probability

$$P_i = \pi p_i + \pi' p_i'$$

in the ith state. The log likelihood is

$$L = \sum_1^s r_i \log (\pi p_i + \pi' p_i'), \qquad \frac{\partial L}{\partial \pi} = \sum \frac{r_i(p_i - p_i')}{\pi p_i + \pi' p_i'} \tag{8.1}$$

$$E\frac{\partial^2 L}{\partial \pi^2} = -E\left\{\sum \frac{r_i(p_i - p_i')^2}{(\pi p_i + \pi' p_i')^2}\right\} = -m \sum \frac{(p_i - p_i')^2}{\pi p_i - \pi' p_i'},$$

so that the estimated variance of $\hat{\pi}$ is

$$V(\hat{\pi}) = 1 \Big/ m \sum \frac{(p_i - p_i')^2}{\hat{\pi} p_i + \hat{\pi}' p_i'}. \tag{8.2}$$

The maximum likelihood estimate $\hat{\pi}$ obtained by setting $\partial L/\partial \pi = 0$ in (8.1) can be found by trial, although this is tedious if the states are numerous. One way of obtaining a first trial value of π is to note that each state furnishes an unbiased estimate. Since

$$E(r_i) = mP_i = m(\pi p_i + \pi' p_i'),$$

the estimate $\hat{\pi}_i$ from the ith state is

$$\hat{\pi}_i = [(r_i/m) - p_i']/(p_i - p_i') : V(\hat{\pi}_i) = P_i Q_i / m(p_i - p_i')^2.$$

These estimates are likely to differ markedly in precision. A fairly good method for a first trial $\hat{\pi}$ is to combine the states for which $p_i > p_i'$, making a single estimate from these states. Table 10 shows a numerical example for a sample of 100 specimens.

From the first two states a trial value is computed as

$$\hat{\pi}_1 = \frac{0.67 - 0.2}{0.6} = 0.78.$$

The values of $r_i(p_i - p_i')$, P_i and $r_i(p_i - p_i')/P_i$ are next computed (Table 10). The total of the latter values gives $\partial L/\partial \pi$ as -5.2. Since

TABLE 10

EXAMPLE OF THE M. L. ESTIMATION OF π (COMPUTED FOR $\hat{\pi} = .78$)

p_i	p_i'	r_i	$r_i(p_i - p_i')$	P_i	$r_i(p_i - p_i')/P_i$
.5	.1	37	14.8	.412	35.9
.3	.1	30	6.0	.256	23.4
.1	.2	9	−0.9	.122	−7.4
.1	.6	24	−12.0	.210	−57.1
		100			−5.2

$\partial L/\partial\pi$ is a decreasing function of π the second trial must be lower. The estimate $\hat{\pi}_2 = 0.75$ gave $+0.5$ for the first derivative. From (8.2) the estimated standard error of $\hat{\pi}_2$ was found to be ± 0.075.

Examination of the formula for the standard error shows that the estimate $\hat{\pi}$ cannot be expected to be precise: the standard error is always larger than the value $\sqrt{\pi(1-\pi)/m}$ that would apply to a binomial estimate of π. This suggests that it will be worthwhile to estimate π only after a substantial number of specimens have been classified.

9. SUMMARY

This paper deals with the problem of assigning specimens to one of two or more universes when the measurements on each specimen are qualitative, each taking a small number of states. After presenting the optimum rule for classifying the specimens, three problems are considered.

The construction of the rule requires initial data on a number of specimens known to be classified correctly. Standard classification theory assumes that these initial samples are infinite in size, although in practice they may be only moderate. The principal effects of the finite sizes of the initial samples are that the probability of misclassification of the rule derived from them is underestimated and that this rule may be inferior to the theoretical optimum rule that we could construct if we had infinite samples. Methods are proposed for obtaining reasonably unbiased estimates of the performance of rules derived from finite samples and for estimating the difference between the actual and the theoretical optimum probability of misclassification. It appears that initial samples of size 50 from each of two universes should be adequate if there are not more than 8 multivariate states. With greater numbers of states, larger sample sizes are needed to ensure

that the actual rule will be almost as good as the theoretical optimum.

If most of the variates are qualitative but a few are continuous, one possibility is to transform the continuous variates into qualitative ones, particularly since classification is easier with qualitative than with continuous variates. Asymptotic results are obtained for the best points of partition and the probabilities of misclassification when a large number of independent normal variates are partitioned to form qualitative variates. For qualitative variates with 2, 3, 4, 5 and 6 states the relative efficiencies are 64, 81, 88, 92 and 94 percent respectively. Computations for small numbers of variates show that the asymptotic points of partition remain satisfactory although the relative efficiencies are in general lower.

The optimum rule depends on the relative frequencies with which specimens to be classified present themselves from different universes. Initial estimates of these frequencies must be made in order to set up the rule. With two universes, maximum likelihood estimates of the frequencies from the data for specimens that have been classified by the rule are given. These estimates enable the rule to be improved if the initial estimates differ from the frequencies that apply when the rule is being used.

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THE STANDARDISATION OF TUBERCULIN HYPERSENSITIVITY

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INTRODUCTION AND SUMMARY

Tuberculin hypersensitivity results from stimulation of the reticulo-endothelial system by tubercle bacilli and is due to the production of sensitised lymphocytes, that is, lymphocytes carrying antibody specific towards tuberculin. The presence of this antibody is detected by the Mantoux Test in which fluid containing tuberculin is injected into the superficial layers of the skin. This intradermal injection forms a bleb which quickly spreads outwards and is absorbed, depositing the tuberculin in the superficial layers. After deposition the tuberculin either escapes into the circulatory system or is reacted upon in situ by the antibody resulting in a final distribution of "reaction products" about the point of injection. It is postulated that induration or hardening of the skin will occur wherever the areal density of these products exceeds a certain level and that this level actually obtains at the edge of induration. In other words the areal density of tuberculin decreases from the point of injection and induration occurs wherever it exceeds a certain minimum level, the Minimum Tuberculin Concentration (c.f. Miles [1949]).

In this paper a mathematical model is presented by which the antibody-level may be calculated from a knowledge of the dose and concentration of tuberculin used and the resultant area of induration, provided this is non-zero. A statistical model of the multi-hit type deals with the antibody-level induced by different amounts of bacillary stimulation and thereby provides a measure of the virulence of the particular tubercle bacillus. The models can be applied to the results of skin-tests for any antibody by means of an appropriate antigen but for convenience they will be explained in the context of data from the Mantoux Test.

R. A. Fisher [1949] made a statistical analysis of the results of intradermal injections in cows in order to standardise different tuber-

TABLE 1

EFFECT OF TUBERCULIN DOSE IN CONSTANT VOLUME ON DIAMETER OF INDURATION

No. of subjects	Diameter mm		Areal Difference
	10 T.U.	1 T.U.	
Group I			
2	11.0	2.0	117
8	12.0	4.0	128
11	12.5	5.0	131
1	12.5	5.5	126
10	12.5	6.0	120
5	13.0	6.5	127
8	13.0	7.0	120
2	13.0	7.5	113
4	13.5	7.0	133
1	13.5	7.5	126
11	13.5	8.0	118
2	14.0	7.0	147
2	14.0	8.0	132
1	14.0	8.5	124
3	14.0	9.0	115
1	14.5	8.5	138
15	14.5	9.0	129
1	14.5	10.0	110
4	15.0	9.5	135
17	15.0	10.0	125
3	15.5	10.0	140
1	15.5	10.5	130
2	15.5	11.0	119
2	16.0	10.5	146
2	16.0	11.0	135
2	16.0	12.0	112
1	16.5	11.5	140
12	16.5	12.0	128
1	17.0	12.0	145
1	18.0	13.5	142
10	18.0	14.0	128
2	18.5	15.0	117
2	19.5	16.0	124
4	20.0	16.0	144
2	20.0	16.5	128
1	20.5	16.5	148
1	22.0	19.0	123
2	23.0	20.0	129
1	27.0	25.0	104

TABLE 1—(*Continued*)

No. of subjects	Diameter mm		Areal Difference
	10 T.U.	1 T.U.	
Group II			
10	12.0	4.5	124
11	12.5	6.0	120
5	14.5	9.0	129
5	15.0	10.0	125
3	20.0	16.0	144
6	20.0	16.5	128

culins. He concluded "the precision of such (tuberculin) readings regarded as biological assay seems to have been much underrated." Our work shows that a similar precision can be revealed by statistical and mathematical analysis for observations on human subjects and guinea-pigs.

EXPERIMENTAL MATERIALS AND METHODS

Tests were made on 260 human subjects and 10 guinea-pigs. The tuberculin was PPD (human) from the Ministry of Agriculture and Fisheries Institute, Weybridge. The B. C. G. was the liquid form from the Danish Serum Institute and the virulent tubercle bacillus was the strain Myc. Tub. H37Rv from the National Institute of Type Cultures. The injection-technique was carefully designed to reduce the error variance of the volumes injected. The diameters of induration were measured to 0.5 mm. at 72 hours after injection.

RESULTS AND THEORY

1. *The relation between induration-area and dose of tuberculin in constant volume*

About 250 subjects were given intradermal injections of 1 and 10 tuberculin units (T. U.'s) in 0.1 ml. Table 1 gives the results of those 161 subjects (Group I) who gave readable non-zero reactions to both doses. Another 40 subjects (Group II), known to be *negative reactors*, were BCG-vaccinated and then tested with 10 and 100 T. U.'s in 0.1 ml. Three levels of BCG-dose were used which explains the bunching of observations in this group.

The square of the diameter of induration D will be called the induration-area, written as D_1^2 , D_{10}^2 , D_{100}^2 for the three tuberculin doses.

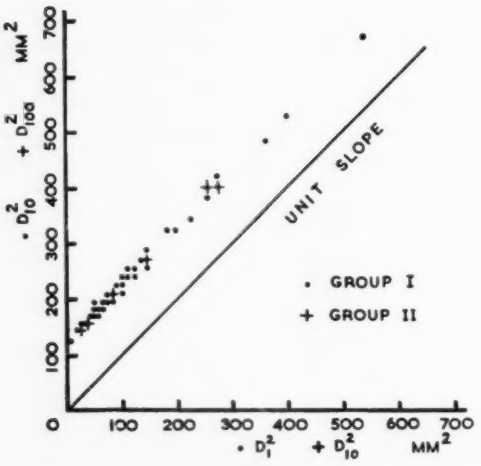

FIGURE 1

THE AREAS OF THE PAIRED TUBERCULIN REACTIONS OF GROUPS I AND II

The areas are plotted in Figure 1. The areal differences A (either $D_{10}^2 - D_1^2$ or $D_{100}^2 - D_{10}^2$) are given in the final column of Table 1. There is no discernible regularity in the A's of either group and 95 percent confidence limits for the difference of their means are -1.4, 3.8. Pooled, their standard deviation of 7.5 is consistent with constancy and an observational error of standard deviation 0.21 mm. For a representative areal difference is derived from reactions of sizes D' and D with means 15 and 10 mms. respectively. Then

$$\delta A \cong 30\ \delta D' - 20\ \delta D$$

$$\text{s.d. } A \cong (900 \text{ var } \delta D' + 400 \text{ var } \delta D)^{1/2} = 7.5.$$

These results suggest that the relation between the induration-area and the dose d of tuberculin in T. U.'s is

$$D^2 = \alpha^* \log d + \beta \qquad (1)$$

where α^* is a constant for all 201 subjects and β is a personal constant containing all the information in the reaction relevant to the subject's sensitivity. The least-squares estimate of α^* is 126.7 (s. d. 0.5). For a given subject the critical dose of tuberculin which will just produce induration is obtained by putting $D = 0$ in equation (1).

Additional confirmation of the equation was provided by testing four subjects with a range of doses in 0.1 ml. The results are given

TABLE 2

THE OBSERVED AND PREDICTED INDURATION AREAS AT CONSTANT VOLUME

Subjects	Dose of PPD in T.U. (d)						
	10	5	2.5	1	0.5	0.25	0.1
1	256	225	196	—	100	—	6
		(218)	(180)		(91)		(3)
2	144	110	72	20	0	0	0
		(106)	(68)	(17)	(0)	(0)	(0)
3	144	110	72	16	0	0	0
		(106)	(68)	(17)	(0)	(0)	(0)
4	110	—	36	—	—	0	0
			(34)			(0)	(0)

in Table 2 where the bracketed figures are the areas predicted from equation (1) with $\alpha^* = 126.7$, using the observed areas at 10 T. U. to estimate β.

2. *Effect of change of volume of injected fluid on* (*i*) *induration-area* (*ii*) *area covered by fluid.*

16 subjects were each given four simultaneous intradermal tuberculin injections, 10 and 1 T. U. in 0.1 and 0.2 ml., and two intradermal injections of Evans blue in volumes of 0.1 and 0.2 ml. The results are given in Table 3 where F is the diameter to which the dyed fluid spread after two hours. For the tuberculin results, at each volume the areal difference A from 1 to 10 T. U. is calculated for the cases when both areas are non-zero. The average of the A's at 0.1 ml. is 133.2 which is not significantly different from 126.7. Half the average at 0.2 ml. is 121.8 which is only 4.9 less than 126.7. The suggestion is that the rate of change of area with log-dose is proportional to the volume of fluid V. (In fact, for all but one subject the A at 0.2 ml. is less than twice the A at 0.1 ml., so that the relation is probably not exact.) Equation (1) can be extended to give

$$D^2 = \bar{\alpha} V \log d + \beta(V). \tag{2}$$

Comparison with equation (1) shows that $\beta(0.1) = \beta$ and $0.1\ \bar{\alpha} = \alpha^*$, so that $\bar{\alpha}$ can be estimated as 1267. For the dye-injections, the results suggest that F^2/V is independent of V or that

$$F^2 = \kappa V. \tag{3}$$

TABLE 3

THE EFFECT OF VOLUME OF INJECTED FLUID ON THE INDURATION-AREA AND THE AREA COVERED BY THE FLUID

Vol. injected fluid, V	0.1 ml.					0.2 ml.				
	Tuberculin			Dye		Tuberculin			Dye	
Subject	10 T.U. Diam.	1 T.U. Diam.	Areal difference	Diam. F	F^2/V or κ	10 T.U. Diam.	1 T.U. Diam.	Areal difference	Diam. F	F^2/V or κ
1	4.0	0.0		20	4000	0.0	0.0		28	3920
2	5.0	0.0		13	1690	0.0	0.0		18	1620
3	7.0	0.0		13	1690	5.0	0.0		18	1620
4	12.5	5.0	131	13	1690	15.5	0.0		18	1620
5	15.0	10.0	125	20	4000	18.5	11.0	221	28	3920
6	15.0	10.0	125	20	4000	19.0	11.0	240	28	3920
7	15.0	10.0	125	20	4000	19.5	11.5	248	28	3920
8	16.5	12.0	128	20	4000	21.5	15.0	237	28	3920
9	16.5	12.0	128	16	2560	22.0	15.0	259	22	2420
10	17.0	12.0	145	20	4000	22.5	16.0	250	28	3920
11	17.0	12.0	145	20	4000	23.0	16.5	257	28	3920
12	18.0	14.0	128	20	4000	24.0	18.0	252	28	3920
13	19.0	15.0	136	20	4000	25.0	19.0	264	28	3920
14	20.0	16.5	128	29	8410	27.0	22.0	245	41	8405
15	23.0	20.0	129	29	8410	31.0	27.0	232	41	8405
16	28.0	25.0	159	29	8410	38.0	35.0	219	41	8405

Model for the deposition of tuberculin

By requiring that $d \exp(-D^2/\bar{\alpha}V \log_{10} e)$ be constant for constant V, equation (2) suggests that the fluid spreads and is absorbed *as if*, before absorption, it assumed the shape of a circular-normal distribution truncated at diameter F and with a variance s^2 proportional to V.

For such a distribution the areal concentration of fluid $f(r)$ at radius r would be

$$f(r) = [V \exp(-\tfrac{1}{2}r^2/s^2)]/2\pi s^2[1 - \exp(-F^2/8s^2)]$$

for $r < \frac{1}{2}F$. If δV is the extra fluid conceptually needed to extend the circular-normal distribution to infinity then

$$V/(V + \delta V) = 1 - \exp(-F^2/8s^2) = \mu$$

say. If $8s^2 = \alpha V$ where α is a constant, then use of equation (3) gives

$$\mu = 1 - \exp(-\kappa/\alpha) \tag{4}$$

so that μ is also a constant. If $t(r)$ is the areal density of deposited tuberculin at radius r in T. U.'s/mm^2, then

$$t(r) = 4d \exp(-4r^2/\alpha V)/\pi\alpha\mu V. \tag{5}$$

Denoting the Minimum Tuberculin Concentration by τ, this will obtain at the edge of induration provided $D < F$; so substituting $r = \frac{1}{2}D$ and $t(\frac{1}{2}D) = \tau$ in equation (5), we obtain

$$D^2 = \alpha V \log_e(4d/\pi\alpha\mu\tau V). \tag{6}$$

When $D = F$, the Minimum Tuberculin Concentration may be exceeded at the edge of induration and equation (6) will not be true. Reference to Table 3 shows that usually $D < F$.

Agreement with the data

Equation (2) agrees with equation (6) when $\bar{\alpha} = \alpha \log_e 10$ and $\beta(V) = \bar{\alpha}V \log(4 \log_e 10/\pi\bar{\alpha}\mu\tau V)$. By equation (4) we find that the four levels of κ represented in Table 3 have corresponding levels of $1 - \mu$ of $10^{-1.3}$, $10^{-2.0}$, $10^{-3.2}$ and $10^{-6.6}$. So for these subjects $\mu \cong 1$ and the relation becomes

$$D^2 = \bar{\alpha}V \log(4d \log_e 10/\pi\bar{\alpha}\tau V) \tag{7}$$

to a good approximation. (It is, however, conceivable that, if more subjects had been examined, smaller values of μ would have been found.) Equation (7) predicts the relationship between D and V when d is held constant. Table 4 gives the results of calculations of $\log \tau$ for the subjects of Table 3. For each subject, the model is supported

by (i) the constancy of the log τ's calculated from non-zero diameters, (ii) the fact that for a zero diameter the log τ calculated by putting $D = 0$ in equation (7) is smaller. From equation (7) it follows that, when V is increased, D^2 will also increase but that a volume is ultimately reached above which D^2 will decrease. When $d = 10$ T. U.'s and log τ exceeds -1.238 or when $d = 1$ T. U. and log τ exceeds -2.238, we would expect the D^2 for 0.1 ml. to *exceed* that for 0.2 ml. The expectation is supported by subjects 1, 2, 3 and 4. For subjects 1 and 2 at 10 T. U.'s and subject 4 at 1 T. U., the effect of increasing V is to dilute the tuberculin so much that at no point in the entire area of the reaction is the Minimum Tuberculin Concentration reached and no induration develops. For subjects 5–16 this dilution effect is more than offset by the increased spread of the fluid which results in tuberculin being carried further from the site of injection at more than the necessary minimum concentration.

3. *Antibody level related to* (*i*) *Minimum Tuberculin Concentration and* (*ii*) *bacillary stimulation.*

(i) Let $t(T)$ be the areal density of tuberculin at a particular point at time T after deposition. The rate of escape of tuberculin into the circulatory system without reaction with antibody will be $[t'(T)]_E = -\epsilon t(T)$ where ϵ is a constant for a given subject (Kety [1949]). If λ is the antibody density, the rate of accumulation of reaction products will be $r'(T) = \lambda t(T)$ and the rate of reaction of tuberculin will be $[t'(T)]_R = -\omega r'(T)$ where ω is a constant. Therefore

$$t'(T) = [t'(T)]_E + [t'(T)]_R = -(\epsilon + \omega\lambda)t(T)$$

$$t(T) = t(0) \exp [-(\epsilon + \omega\lambda)T]$$

$$r(T) = \lambda t(0)\{1 - \exp [-(\epsilon + \omega\lambda)T]\}/(\epsilon + \omega\lambda)$$

$$r(\infty) = \lambda t(0)/(\epsilon + \omega\lambda).$$

If induration occurs wherever $r(\infty) > \rho$ then

$$\tau = \gamma/\lambda + \delta \tag{8}$$

where $\gamma = \epsilon\rho$ and $\delta = \omega\rho$.

(ii) *The multi-hit model.*

Injected (or otherwise acquired) bacilli will be distributed throughout the reticulo-endothelial tissues which consist of *lymphocyte-producing centres.* The bacilli stimulate these centres to pour sensitised lymphocytes (antibody) into the circulation. Suppose (a) the bacilli are

distributed randomly among a much larger number of centres, (b) at least ν bacilli are required to sensitise a centre, (c) the resulting λ is proportional to the number of sensitised centres. If B bacilli are distributed among C centres and $p_r(B)$ and $s_r(B)$ are the mean proportions of centres with r and r or more bacilli respectively, then

$$Cs_r(B+1) - Cs_r(B) = p_{r-1}(B) \qquad r = 1, 2, \cdots$$

or approximately, when B is large,

$$Cs_r'(B) = s_{r-1}(B) - s_r(B).$$

Therefore

$$\left(C\frac{d}{dB} + 1\right)^r s_r(B) = s_0 = 1$$

the solution of which is

$$\begin{aligned} s_r(B) &= 1 - e^{-B/C}[1 + (B/C) + \cdots + \{1/(r-1)!\}(B/C)^{r-1}] \\ &= e^{-B/C}[(1/r!)(B/C)^r + \{1/(r+1)!\}(B/C)^{r+1} + \cdots]. \end{aligned}$$

TABLE 4

LOG MINIMUM TUBERCULIN CONCENTRATION (τ)

Injection-volume	0.1 ml.		0.2 ml.		Average log τ	$\bar{\kappa}$
Dose of PPD	10 T.U.	1 T.U.	10 T.U.	1 T.U.		
Subject						
1	−0.76	(−1.64)	(−0.94)	(−1.94)	−0.76	3960
2	−0.83	(−1.64)	(−0.94)	(−1.94)	−0.83	1655
3	−1.02	(−1.64)	−1.04	(−1.94)	−1.03	1655
4	−1.87	−1.83	−1.88	(−1.94)	−1.86	1655
5	−2.41	−2.42	−2.29	−2.41	−2.38	3960
6	−2.41	−2.42	−2.36	−2.41	−2.38	3960
7	−2.41	−2.42	−2.44	−2.46	−2.43	3960
8	−2.78	−2.77	−2.76	−2.82	−2.78	3960
9	−2.78	−2.77	−2.85	−2.82	−2.80	2490
10	−2.92	−2.77	−2.93	−2.95	−2.89	3960
11	−2.92	−2.77	−3.02	−3.01	−2.93	3960
12	−3.19	−3.18	−3.21	−3.22	−3.20	3960
13	−3.48	−3.41	−3.40	−3.36	−3.41	3960
14	−3.79	−3.78	−3.81	−3.85	−3.81	8408
15	−4.81	−4.79	−4.73	−4.81	−4.78	8408
16	−6.82	−6.57	−6.64	−6.77	−6.70	8408

If B/C is small, we therefore expect $\lambda \propto B^{\nu}$ or

$$\log \lambda = \nu \log B + \eta \tag{9}$$

where η is a constant. The integer ν provides the measure of bacillary virulence.

Agreement with data.

(i) *Human Subjects.* 39 female subjects, whose preliminary skin-tests showed no induration, were vaccinated with a range of B. C. G. doses and after six weeks were tested with 100 T. U.'s in 0.1 ml. The log τ's calculated from equation (7) are given in Table 5. Each subject's B. C. G. dose establishes a level of λ. Table 5 shows that the variance

TABLE 5

EFFECT OF B.C.G. DOSE ON SIZE OF INDURATION

No. of subjects	Vol. B.C.G. in ml.	Induration diameter (mms)	log τ	Average log τ
2	0.300	32.0	−7.72	−7.80
1	0.300	32.5	−7.97	
2	0.250	30.0	−6.74	−6.90
1	0.250	31.0	−7.22	
1	0.245	28.0	−5.82	−6.16
1	0.245	29.5	−6.50	
1	0.155	25.5	−4.77	−4.77
1	0.150	24.0	−4.18	−4.47
3	0.150	25.0	−4.57	
1	0.140	24.0	−4.18	−4.18
1	0.130	23.0	−3.81	−3.81
2	0.120	22.0	−3.46	
1	0.120	22.5	−3.63	−3.59
1	0.120	23.0	−3.81	
1	0.100	20.0	−2.79	−2.79
1	0.080	16.0	−1.66	−1.79
1	0.080	17.0	−1.92	
1	0.075	14.5	−1.30	
3	0.075	15.0	−1.41	−1.41
1	0.075	15.5	−1.53	
2	0.070	14.0	−1.18	−1.30
1	0.070	15.5	−1.53	
1	0.065	12.0	−0.77	−0.77
3	0.060	10.0	−0.43	
2	0.060	10.5	−0.51	−0.51
3	0.060	11.0	−0.59	

of Minimum Tuberculin Concentrations within dose-levels is much smaller than the between-dose variance. This implies that the constants γ and δ differ only slightly, if at all, among these subjects. If δ is constant from subject to subject, it is clear from equation (8) that it is less than any τ occurring. Therefore $\delta < 10^{-7.97}$. The average of

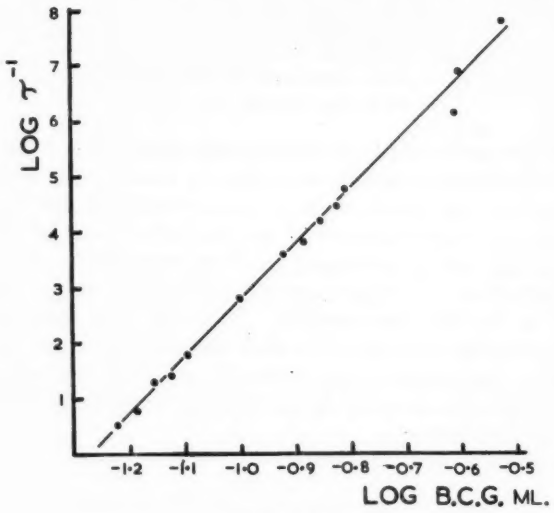

FIGURE 2

THE EFFECT OF B.C.G. DOSE ON THE MINIMUM TUBERCULIN CONCENTRATION

log τ^{-1} is plotted against the log B. C. G.-dose in Figure 2. The least-squares straight-line has the equation

$$\log \tau^{-1} = 10.1 \log B.C.G. + 12.9. \tag{10}$$

(95 percent confidence limits for the slope are 9.8, 10.4. A significantly better fit is possible by allowing a quadratic term but the improvement is only slight.) It is reasonable to extrapolate and state that higher B. C. G. doses would result in much lower τ's than 10^{-8} T. U.'s/(mm)^2. So for all subjects we will put $\delta = 0$ in equation (8) and write

$$\tau = \gamma/\lambda. \tag{11}$$

Since $\gamma = \epsilon\rho$ and $\delta = \omega\rho$, the interpretation of $\delta \cong 0$ is that most of the tuberculin escapes without local reaction.

As stated above, the variance of γ from subject to subject must

be quite small. This is somewhat surprising since γ is presumably related to skin-type. However, all 39 subjects were aged 18 or 19 so that perhaps γ is determined by age. The subjects of Table 4 throw some light on this. The relation of the *area of fluid coverage* constant κ with age is as follows:

$\kappa = 1655$, ages over 65;
$\kappa = 2490$, age 55;
$\kappa = 3960$, ages between 30 and 45;
$\kappa = 8408$, ages under 30.

The negative correlation is statistically significant ($P = 0.05$). There is a (non-significant) negative correlation of κ and τ. Accepting both correlations as real, there would be two possibilities consistent with the theory: (i) γ is independent of age but both κ and λ decrease with age, the latter due to decreasing bacillary stimulation. In this case the determination of κ by dye-injection has no relevance to the interpretation of the Mantoux reaction. (ii) γ and κ are correlated, both being functions of skin-type. The data considered does not distinguish these two. One experimental approach would be to take *negative reactors* at different ages and induce possibly identical antibody levels by B. C. G. vaccination.

Equations (10) and (11) combine to give

$$\log \lambda = 10.1 \log B.C.G. + 12.9 + \log \gamma.$$

The confidence interval for the slope includes the value 10 so that the results are consistent with equation (9) when $\nu = 10$.

(ii) *Guinea-pigs.*

Each of five dose-levels of virulent Myc. Tub. bacilli was given by intraperitoneal injection to one of five pairs of guinea-pigs. The animals were tested with 100 T. U.'s in 0.1 ml. on the 10th, 18th, 27th and 35th days after injection. On one occasion each pair was also tested with 320 T. U.'s. The average diameters for each pair are given in Table 6 with the 320 T. U. results in brackets. The simultaneous diameters at 100 T. U. and 320 T. U. are consistent with equation (1) with the same value of α^* as for humans 126.7. For the differences $D^2_{320} - D^2_{100}$ are 56, 56, 61, 66 and 69 with an average of 62. By equation (1) the difference should be 64. If equations (7) and (11) also hold, the antibody levels, $\log(\lambda/\gamma)$, can be calculated. These are plotted in Figure 3. For these animals the bacillary content is increasing with time. If the increase is geometric, the actual bacillary content

TABLE 6

THE INDURATION DIAMETERS PRODUCED BY DIFFERENT DOSES OF MYCOBACTERIUM TUBERCULOSIS (H 37 Rv) IN GUINEA-PIGS

Days after infection	Dose of infecting organisms; Log mgms. wet weight of bacilli				
	−1.796	−1.893	−1.990	−2.087	−2.184
10	9	8	5	2	0
18	10	9	7	5 (9)	0
27	11	10 (12.5)	8.5	7	5
35	12 (14.5)	11	10 (13)	8.5	7 (10.5)

on the Tth day will be $B_0 10^{kT}$ where B_0 is the initial dose and k is the growth-rate constant. If equation (9) holds, then

$$\log (\lambda/\gamma) = \nu \log B_0 + \nu k \log T + \text{const.}$$

The least-squares estimates are $\hat{\nu} = 2.05$, $\hat{k} = 0.0104$ and $\widehat{\text{const.}} = 3.72$. The lines drawn in Figure 3 are based on these estimates. In view of the small number of observations a slope of 2.05 is consistent with a true value of ν of 2.

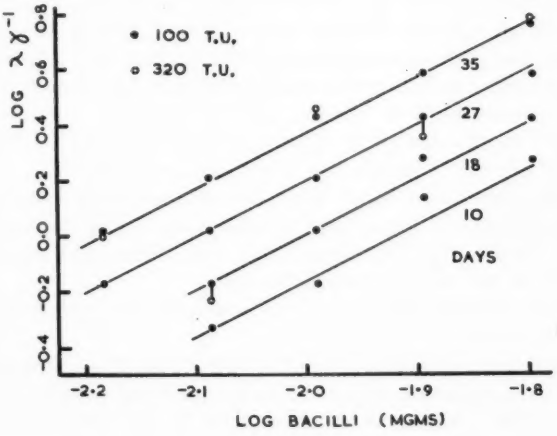

FIGURE 3

THE RELATION BETWEEN ANTIBODY LEVEL AND INFECTING DOSE OF MYC. TUB. (H 37 Rv) AT 10, 18, 27 AND 35 DAYS AFTER INJECTION

If the models are valid, it must be concluded that, whereas at least 10 B. C. G. bacilli are needed to activate a lymphocyte-producer in humans, only two virulent Myc. Tub. bacilli are required in guinea-pigs.

DISCUSSION

The conclusion of Section 1 of Results was that there exists a linear relation between the induration-area and the log-dose of tuberculin in constant volume. This contradicts the conclusion of Long and Miles [1950] with tuberculin and of Miles [1949] with diphtheria toxin that the linear relation is between *diameter* and log-dose. In Long and Miles [1950] it is stated that Wadley [1948, 1949] had found such a relation. However examination of Wadley's paper shows that the bulk of the work established a linear relation between log-dose and the *increase in thickness* of the induration produced by tuberculin injection in cattle. Miles [1949] rests the case for his linearity on visual inspection and analyses of variance. In his Table 1 there is a statistically significant departure from linearity but the associated F-value is small compared with that for the linear component. However, provided the range of reaction-diameters is not too large, this may also be expected to result from our equation (1). For example, with five doses at two-fold dilution intervals and the diameters ranging from 10 to 17.5 mms, the mean square for linearity would be several hundred times larger than the mean square for departures from linearity. In other words for this range the two theories are not clearly distinguishable. Miles observes, and it is apparent from his figures, that the departures from linearity tended to occur with small induration-diameters—"the curves dipping more steeply to the 3–5 mm values". He invokes a special argument in explanation of this. However this kind of departure is precisely what our equation (1) would lead us to expect.

In this paper an attempt has been made to present a validation of two models without considering whether they can be justified on more general grounds. A fuller discussion of their clinical and immunological implications will be published elsewhere.

Further experimentation is clearly needed to deal with such questions as the following:

(i) Are the constants or even the form of the dose-response relation of the intradermal test dependent on experimental technique?

(ii) Is the multi-hit model correct for bacilli other than BCG and the Mycobacterium Tuberculosis used?

(iii) Is the approach adopted useful for diseases other than tuberculosis?

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OPTIMUM ESTIMATION OF GRADIENT DIRECTION IN STEEPEST ASCENT EXPERIMENTS

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Summary

In the steepest ascent method for seeking maxima (Box and Wilson), the procedure involves the progression to a region of high response by successive inferences as to the gradient direction in sets of trials en route. When there is no experimental error, and the response surface is well approximated by a plane in any locality, then it can be seen that an appropriately patterned set of trials, numbering just one more than the number of factors, would be required to completely characterize this plane and thus the gradient direction. Were there experimental error, however, the gradient direction would be correspondingly uncertain. One wonders whether to expect that more ground would be gained by having more trials in each set at the expense of having fewer sets. As this problem is formulated herein, there is a strong conclusion that the number of trials per set should be minimal.

I. *Introduction*

The procedure of steepest ascent (Box and Wilson, [1951]) consists of performing a sequence of sets of trials. Each set of trials is "centered" at a combination of factor levels, or point in factor space. An initial point is selected for the center of the first set of trials. Succeeding center points are determined by estimating the appropriate relative changes among the factor levels, i.e., the direction of the change, from the results of the set of trials just performed and scaling the increments of change such that the new center point is a fixed distance, the step length, away from the old. This procedure is followed until a near stationary region is attained.

This investigation is concerned with the allocation of effort to the trials in the initial stages of the search, where one is not likely to be close to a point of maximum response. It is assumed that the choice of scales for the factor levels has been decided upon, so that a distance is defined, and that a step length has been selected. The purpose of a set of trials is (and we here regard this as the sole purpose) then to

supply the direction of the "step" for determining the next center point. Box and Wilson [1951] have shown that the appropriate direction is that of the gradient at the new point. Consequently the purpose of a set of trials is to provide an estimate of the gradient direction.

It is assumed that the response surface is well approximated by a plane in any locality. Then the gradient direction estimated as a result of a set of trials differs from that of the true gradient by some angle, say θ, when there is experimental error. The greater the number of trials in a set, the smaller θ is expected to be. Let us designate by S the size of step to be taken in the estimated gradient direction. As a result, $S \cos \theta$ is the component of this step which is in the direction of the true gradient. If $\cos \theta$ were near to one, the gradient would be well estimated and the step would be well taken. If $\cos \theta$ were near zero, there would be comparatively little change in the response to be expected. If $\cos \theta$ were negative, the step would be downhill. Thus, $S \cos \theta$ may be regarded as the improvement in position in factor space as a result of a set of trials.

Let us regard a trial as a unit of effort, so that for t trials in a set, the improvement per unit of effort is $(S \cos \theta)/t$. In planning a set of trials it is desirable to select t so as to maximize the expected value of the improvement per unit effort, i.e. $E[(S \cos \theta)/t]$. This is equivalent to selecting t so as to maximize $(1/t)\, E(\cos \theta)$, where $E(\cos \theta)$ is regarded as a function of t.

Our main result is that the maximum is achieved when t is one more than the number of factors; that is, it is not worthwhile to improve the precision of the estimate of the gradient direction at the expense of more trials. Since this result would be anticipated if the experimental variation could be ignored, it is of interest that it applies independently of the magnitude of the variability. The result is convenient from the point of view of application, since otherwise the appropriate value of t would depend upon the magnitude of the gradient and upon the experimental variability, the ratio of which would have to be estimated in advance of the set of trials. Consequently, the simplicity of the result enhances its value.

The result is developed from the assumption that the trial design yields normally distributed uncorrelated estimates of the gradient components which have the same variance. The magnitude of the common variance will depend upon the design used. Although the present result does not evaluate the relative efficiency of alternative designs, the above formulation of the problem does provide a basis for comparison by means of $E(\cos \theta)$. While we do not pursue this line of investigation here, some tabular values are given, so that alternative

designs can be readily compared from the point of view of efficiency for maxima seeking.

The basic function $E(\cos\theta)$ is evaluated in Section II, and some numerical values are presented. The development is completed in Section III by applying the result of Section II to establish the main result of the paper. Some numerical values are presented of how the efficiency depends on the number of trials within a set.

Brief mention should be made of related aspects of the maximum seeking problem that our formulation has not considered. The problem of recognizing that a near stationary region has been reached may present difficulties in the case of large experimental error. Another aspect is the effect of the curvature of the response surface both on the selection of the design of a set of trials and the size of the region over which the design is to be applied and consequently on the estimation of the gradient direction. Finally, we note that the prior selection of scales of the factor levels and step length also affect the estimate of the gradient direction.

II. *Derivation of* $E(\cos\theta)$

Let us suppose that in the vicinity of a set of trials the relation between the response and the n factors is well represented by a plane:

$$R = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \epsilon,$$

where x_i is the level of the ith factor and ϵ is the experimental error,[1] $NID(0, \sigma_\epsilon^2)$.

Let us suppose, also, that as a result of a set of t trials it is possible to construct an estimate b_i of β_i such that the b_i are $NID(\beta_i, \sigma^2)$ and σ^2 is a function of t.

The angle between the true gradient β, having components β_i, and the estimated gradient b, having components b_i, is θ. Consequently:

$$\cos\theta = \sum b_i\beta_i / \sqrt{\sum b_i^2 \sum \beta_i^2} \quad \text{where} \quad 0 \leq \theta \leq \pi.$$

$E(\cos\theta)$ is to be found from the joint distribution of the magnitude and angle of error, θ of the random vector b. It is possible to orient the factor space so that, without loss of generality, the components of β may be expressed, in units of σ, as $\rho, 0, 0, \cdots, 0$. Under the same transformation the components of b are $y_1, y_2, \cdots, y_n$. The y_i are NID with

$$E(y_i) = \begin{cases} \rho & i = 1 \\ 0 & \text{Otherwise} \end{cases}$$

[1] NID $(0, \sigma_\epsilon^2)$ means normally and independently distributed with mean zero and variance σ_ϵ^2.

and each with unit variance. The magnitude of b, in units of $\frac{1}{\sigma}$, is r. The joint distribution of r and θ is found from the joint distribution of the y_i :

$$dF(y_i) = (2\pi)^{-n/2} e^{-1/2[(y_1-\rho)^2+y_2^2+\cdots+y_n^2]}\, dy_1\, dy_2 \cdots dy_n .$$

Noting that the quantity in the brackets can be expressed by the cosine law, this function, in terms of θ and r, becomes:

$$dF(r, \theta) = (2\pi)^{-n/2} e^{-1/2(r^2-2r\rho\cos\theta+\rho^2)} r\, d\theta\, dr\, dH,$$

where dH is the region over which r and θ are constant; that is, the surface "area" of an $(n-1)$-dimensional hypersphere of radius $r \sin\theta$. By integration over this region:

$$dF(r, \theta) = \frac{r^{n-1}(\sin\theta)^{n-2}}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{n-1}{2}\right)2^{(n-2)/2}} e^{-1/2(r^2-2r\rho\cos\theta+\rho^2)}\, dr\, d\theta.$$

This provides an expression for the expected value of $\cos\theta$:

$$E(\cos\theta) = \int_{\theta=0}^{\pi}\int_{r=0}^{\infty} \cos\theta\, dF(r, \theta).$$

Expanding $e^{r\rho\cos\theta}$ in powers of $r\rho\cos\theta$ leads to:

$$E(\cos\theta) = e^{-\rho^2/2} \sum_{j=0}^{\infty} \frac{\rho^j}{j!} \int_0^{\pi} \frac{(\cos\theta)^{j+1}(\sin\theta)^{n-2}}{\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{n-1}{2}\right)2^{(n-2)/2}}\, d\theta \int_0^{\infty} r^{n+j-1} e^{-r^2/2}\, dr.$$

Each of the even j terms in the above expression are zero since, for even j,

$$I \equiv \int_0^{\pi} (\cos\theta)^{j+1}(\sin\theta)^{n-2}\, d\theta = 0.$$

For odd j this I integral may be put in the form of the beta function by letting $X = \sin^2\theta$:

$$I = 2\int_0^{\pi/2} (\cos\theta)^{j+1}(\sin\theta)^{n-2}\, d\theta$$

$$= \int_0^1 (1-X)^{j/2} X^{(n-3)/2}\, dX = \frac{\Gamma\left(\frac{j+2}{2}\right)\Gamma\left(\frac{n-1}{2}\right)}{\Gamma\left(\frac{j+n-1}{2}\right)}.$$

The r integral evaluated as a gamma function becomes:

$$2^{(n+j-2)/2}\Gamma\left(\frac{n+j}{2}\right).$$

TABLE 1

EXPECTED VALUE OF COS θ FOR n, THE NUMBER OF FACTORS, AND FOR ρ, THE MAGNITUDE OF THE TRUE GRADIENT RELATIVE TO THE STANDARD ERROR OF AN ESTIMATED COMPONENT AS COMPUTED FROM THE EXACT FORMULA

Number of Factors, n	True gradient ρ (in units of the standard error of component estimation)							
	0.0	0.25	0.50	1	2	4	8	∞
2	0.0000	0.1554	0.3038	0.5572	0.8443	0.9669	0.9921	1.0000
4	0.0000	0.1769	0.2302	0.4342	0.7140	0.9109	0.9768	1.0000
8	0.0000	0.0854	0.1692	0.3266	0.5759	0.8250	0.9482	1.0000
16	0.0000	0.0614	0.1222	0.2395	0.4447	0.7097	0.8984	1.0000
32	0.0000	0.0438	0.0874	0.1729	0.3317	0.5773	0.8186	1.0000

Assembling these terms and letting $j = 2i + 1$, there results:

$$E(\cos\theta) = e^{-\rho^2/2} \sum_{i=0}^{\infty} \frac{\Gamma\left(\frac{2i+3}{2}\right) 2^{(2i+1)/2} \Gamma\left(\frac{n+1}{2}+i\right) \rho^{2i+1}}{(2i+1)!\,\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{n+2}{2}+i\right)}$$

$$= \frac{\rho}{\sqrt{2}} e^{-\rho^2/2} \sum_{i=0}^{\infty} \frac{\Gamma\left(\frac{n+1}{2}+i\right)\left(\frac{\rho^2}{2}\right)^i}{\Gamma\left(\frac{n+2}{2}+i\right) i!}.$$

It may be noted that the above expression is closely related to the confluent hypergeometric function.

An approximation to $E(\cos\theta)$ follows directly from the expression given for $\cos\theta$ by noting that

$$E(\sum b_i\beta_i) = \sum \beta_i^2 = \rho^2\sigma^2,$$
$$E(\sum b_i^2) = (n + \rho^2)\sigma^2.$$

By substituting expected values for the random variables one obtains:

$$E(\cos) \cong \rho/\sqrt{n + \rho^2}.$$

This approximation is in good agreement with the values in the table and illustrates the general nature of this function.[3]

III. *Optimum Number of Trials in a Set*

In the previous section it was stated that ρ is in units of σ and that σ is a function of t. $E(\cos\theta)$ is to be expressed as a function of t so that $(1/t)E(\cos\theta)$ can be examined for the t which maximizes this quantity; that is, the number of trials in a set which results in the greatest expected improvement per unit of effort.

Since the β_i are ordinarily estimated by means of linear functions of the observations, then σ^2 would ordinarily be a simple multiple of σ_ϵ^2. Were that set of trials replicated, say m times, then σ^2 would be the same multiple of σ_ϵ^2/m, which would be proportional to σ_ϵ^2/t. Under these circumstances σ^2 would be proportional to $1/t$. It is suggested that this would be a good approximation of the functional relation of σ^2 and t for more varied experimental designs than those which are replicated, as long as the trials would be made in the same locality. Consequently, since ρ^2 is in units of σ^2, ρ^2 is proportional to t. It is

[3] It can be shown that a lower bound for $E(\cos\theta)$ is $\rho/\sqrt{n + \rho^2 + 1}$.

convenient to work with a quantity which is proportional to t and therefore to ρ^2. Let T, k and $h_n(T)$ be defined by the following:

$$T \equiv kt \equiv \rho^2/2,$$

$$(1/t)E(\cos\theta) = h_n(T) \equiv ke^{-T} \sum_{i=0}^{\infty} \frac{\Gamma\left(\frac{n+1}{2}+i\right)T^{(i-1/2)}}{\Gamma\left(\frac{n+2}{2}+i\right)i!}.$$

As a result of differentiating this with respect to T:

$$\frac{dh_n(T)}{dT} = -\frac{1}{2T}h_n(T) - h_n(T) + h_{n+2}(T)$$

$$= -\frac{1}{2T}h_n(T) - ke^{-T} \sum_{i=0}^{\infty} \frac{\Gamma\left(\frac{n+1}{2}+i\right)T^{i-1/2}}{(n+2+2i)\Gamma\left(\frac{n+2}{2}+i\right)i!}.$$

It is apparent that for any positive n and any positive T, t or ρ^2, this derivative is negative. Consequently, $(1/t)\ E(\cos\theta)$ is a decreasing function of t, so that t should be as small as possible. The minimum number of trials required to estimate a gradient by means of uncorrelated estimates of its components is one more than the number of factors. As a result, $t = n + 1$ is the "optimum" number of trials to be used in each set of a maximum seeking experiment when such estimation is to be done.

The simplex designs are very appropriate for this kind of experimentation. These and other useful first order designs are discussed in the reference by Box. In those cases where the factors can be assigned only discrete levels, the designs given by Plackett and Burman can be used.

IV. *Efficiency of Replication*

It is of interest to see how efficient more than $n + 1$ trials in a set would be since other considerations may make it desirable to do as many trials as would be worthwhile within a single set. This would be the case, for example, if in some agricultural applications, many trials may be carried out simultaneously, but it takes an entire growing season to do any set of trials.

As a notational convenience, the number of trials for which $t = n + 1$ is designated as a single replicate, $R = 1$, and $t = R(n + 1)$ is an Rth replicate. Let G be the value of ρ when $R = 1$. Thus, G is the magni-

tude of the gradient relative to the standard error of estimation of a component when the number of trials used to do this estimation is $n + 1$. For those experimental designs for which the standard error of component estimation is reduced in proportion to $R^{-1/2}$, e.g. "pure" replication, there results the relation $\rho = R^{1/2}G$. The efficiency of

TABLE 2

EFFICIENCY OF R, THE NUMBER OF REPLICATES, FOR n, THE NUMBER OF FACTORS AND G, THE MAGNITUDE OF THE GRADIENT RELATIVE TO THE STANDARD ERROR OF ESTIMATION WHEN $R = 1$

The Number of Factors is $n = 2$

	Relative Magnitude of the Gradient					
Replicates, R	0.25	0.5	1	2	4	∞
1	1.000	1.000	1.000	1.000	1.000	1.000
2	0.702	0.686	0.621	0.550	0.510	0.500
4	0.489	0.459	0.369	0.286	0.257	0.250
8	0.334	0.292	0.203	0.146	0.129	0.125
16	0.224	0.174	0.106	0.073	0.065	0.0625

The Number of Factors is $n = 8$

	Relative Magnitude of the Gradient, G					
Replicates, R	0.25	0.5	1	2	4	∞
1	1.000	1.000	1.000	1.000	1.000	1.000
2	0.705	0.699	0.676	0.618	0.547	0.500
4	0.495	0.482	0.411	0.358	0.287	0.250
8	0.346	0.326	0.272	0.196	0.149	0.125
16	0.239	0.213	0.158	0.103	0.076	0.0625

The Number of Factors is $n = 32$

	Relative Magnitude of the Gradient, G					
Replicates, R	0.25	0.5	1	2	4	∞
1	1.000	1.000	1.000	1.000	1.000	1.000
2	0.706	0.704	0.697	0.672	0.614	0.500
4	0.499	0.495	0.480	0.435	0.354	0.250
8	0.351	0.345	0.322	0.267	0.196	0.125
16	0.247	0.237	0.209	0.154	0.105	0.0625

an Rth replicate for particular n and G is defined as the improvement per unit of effort expected as a result of the Rth replicate design as compared with the improvement per unit of effort expected when $R = 1$

$$\text{Efficiency of } (R \mid n, G) = \frac{\frac{1}{R} E(\cos \theta \mid n, \rho = \sqrt{R}G)}{E(\cos \theta \mid n, \rho = G)}.$$

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A STOCHASTIC STUDY OF THE LIFE TABLE AND ITS APPLICATIONS

III. THE FOLLOW-UP STUDY WITH THE CONSIDERATION OF COMPETING RISKS[1,2]

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INTRODUCTION

Statistical studies falling into the general category of life testing and medical follow-up have as their common immediate objective the estimation of life expectation and survival rates for a defined population at risk. Usually such a study must be brought to a close before all the information on survival (of patients, electric bulbs, automobiles, etc.) is complete, and thus the study is said to be truncated. Whether the investigation is basically concerned with life testing or with medical follow-up, the nature of the problem is the same, although differences in sample size may call for different approaches. Thus methods developed for life testing may be applied to follow-up studies when the underlying conditions are met, and vice versa. In this study cancer survival data utilizing a large sample will be used as illustrative material, and we shall accordingly use the terminology of the medical follow-up study as a matter of convenience.

We are concerned then with a typical follow-up study in which a group of individuals with some common morbidity experience are followed from a well-defined zero point, such as date of hospital admission. Perhaps we wish to evaluate a certain therapeutic measure by comparing the expectation of life and survival rates of treated and untreated patients. Or we may wish to compare the expectation of life of treated and presumably cured patients with that of normal persons. When the period of observation is ended, there will usually remain a number of individuals on whom the mortality data in a typical study will be incomplete. Of first importance among these are the

[1]This study was completed while the author was a Special Research Fellow of the National Heart Institute, Public Health Service, U. S. Department of Health, Education and Welfare.

[2]Parts of this paper were presented at the joint meeting of the American Statistical Association, the Institute of Mathematical Statistics, and the Biometric Society in Washington, D. C., December 29, 1959.

persons still alive at the close of the study. Secondly, if the investigation is concerned with mortality from a specific cause, the necessary information is incomplete and unavailable for patients who died from other causes. In addition, there will usually be a third group of patients who were "lost" to the study because of follow-up failure. These three groups present a number of statistical problems in the estimation of the expectation of life and survival rates. Many significant studies have been made along these lines, among them the early works of Greenwood [13] and Karn [17], the actuarial method of Berkson and Gage [1], a stochastic model of competing risks by Fix and Neyman [12], the parametric studies by Berkson and Gage [2] and Boag [3], the non-parametric approach of Kaplan and Meier [16], studies on life testing by Epstein and Soble [10] and other interesting works by Dorn [3], Elveback [9], Fix [11], Harris, Meier and Tukey [14], and Littell [18].

The purpose of this paper is to adapt the biometric functions of the life table to the special conditions of the follow-up study. Part I considers the general type of study in which survival experience is investigated without specification as to the cause of death. An exact formula will be presented for the maximum likelihood estimator of the probability of death and its asymptotic variance. Special attention will be given to a method for computing the observed expectation of life in truncated studies and the corresponding variance. In Part II the discussion will be extended to apply to studies of mortality from a specific cause in the presence of competing risks. The relations between net, crude, and partial crude probabilities will be reviewed and formulas developed for their estimators and the corresponding variances and covariances. In the last part of the paper, data obtained from the California State Department of Public Health will be used to illustrate the application of the theoretical matter presented in Parts I and II.

Throughout this paper we shall assume that all individuals in a sample are subject to the same force of mortality (or, instantaneous death probability), and that the probability of dying for one individual is not influenced by the death of any other individual in the group. This is to say that the life-times of all individuals in a group are treated as independent and identically distributed random variables. We shall also assume in Part I that there will be no individuals lost to observation because of follow-up failure. The problem of lost cases will be considered in Part II (Remark 3).

For simplicity of presentation, a constant time interval (year) will be used. However, the methods developed in this paper apply equally well to cases where intervals are of different lengths; although the ob-

served expectation of life will have a slightly different form (Cf. [5] and [6]).

The probability symbols used in this paper are listed below for convenient reference. Considering death without specification to cause:

p_x = Pr [an individual alive at time x will survive the interval $(x, x + 1)$],

q_x = Pr [an individual alive at time x will die in the interval $(x, x + 1)$],

and obviously $p_x + q_x = 1$. When death is studied by cause, or risk, we have the net probabilities:

q_{xk} = Pr [an individual alive at time x will die in the interval $(x, x + 1)$ if risk R_k is the only acting risk of death in the population],

$q_{x.k}$ = Pr [an individual alive at time x will die in the interval $(x, x + 1)$ if risk R_k is eliminated from the population];

the crude probability:

Q_{xk} = Pr [an individual alive at time x will die from cause R_k in the interval $(x, x + 1)$, in the presence of all other risks in the population];

and the partial crude probabilities:

$Q_{xk.1}$ = Pr [an individual alive at time x will die from cause R_k in the interval $(x, x + 1)$, when only risk R_1 is eliminated from the population],

$Q_{xk.12}$ = Pr [an individual alive at time x will die from cause R_k in the interval $(x, x + 1)$, when risks R_1 and R_2 are eliminated from the population].

PART I. THE ESTIMATION OF THE PROBABILITY OF SURVIVAL AND EXPECTATION OF LIFE

1.1. *The basic random variables and their joint probability function.*

Consider a follow-up study conducted over a period of y years. A total of N_0 individuals are accepted into the study at any time prior to the closing date[3] and are observed until death or until the study is terminated, whichever comes first. If we set the time of entrance into

[3]Although we have used the common closing date method to illustrate the techniques developed in this paper, it should be pointed out that these techniques are equally applicable to the date of last reporting method.

the study as the common point of origin for all N_0 individuals, then N_0 is taken to be the number with which the study began, or the number of individuals alive at time zero. Let x be the exact number of years since entrance into the study, and N_x the number of individuals who survive to the common point x. Clearly, N_x may also be defined as the number of survivors who entered the study at least x years before its closing date. The number of survivors will decrease as x increases, not only because of deaths but also because of withdrawals due to the closing of the study. We will describe this process of depletion systematically for the typical interval $(x, x + 1)$ with reference to Table 1.[4]

At time x, the N_x survivors who begin the interval can be divided into two mutually exclusive groups according to their date of entrance into the study. A group of m patients entered the study more than $x + 1$ years before the closing date of the study. Out of these, δ patients will die in the interval and s will survive to begin the next interval. The second group of n patients entered the study less than $x + 1$ years before its termination, and hence are all counted as withdrawals

TABLE 1

DISTRIBUTION OF N_x PATIENTS ACCORDING TO WITHDRAWAL STATUS, SURVIVAL STATUS, AND CAUSE OF DEATH IN THE INTERVAL $(x, x + 1)$*

Survival status and cause of death	Withdrawal status in the interval		
	Total number of patients	Number not due for withdrawal**	Number due for withdrawal***
Total	N_x	m	n
Survivors	$s + w$	s	w
Deaths, all causes	D	δ	ϵ
Cause of death			
R_1	D_1	δ_1	ϵ_1
R_2	D_2	δ_2	ϵ_2
	.	.	.
	.	.	.
.	.	.	.
R_c	D_c	δ_c	ϵ_c

*The subscript x, which should be added to each of the symbols in the table, is deleted to simplify formulas in the text.

**Patients admitted to the study more than $(x + 1)$ years before closing date.

***Patients admitted to the study less than $(x + 1)$ years but more than x years before closing date.

[4]The second part of Table 1, death by cause, was included for use in Part II of this paper.

in the interval $(x, x + 1)$, whether or not they survive, because for them the closing date precedes their $(x + 1)$-anniversary date. Let us say that ϵ will die before the closing date and w will survive to withdraw alive.

Thus s, δ, w, and ϵ are the basic random variables (upper part of Table 1) whose distribution depends on the force of mortality. The values that these random variables take on will be used to estimate the probability p_x that a patient will survive the interval $(x, x + 1)$, and its complement q_x, the probability of death in the interval. The first step is to derive the joint probability function of these random variables.

Let μ_τ, a function of time τ, be the force of mortality acting on each individual in the study, such that

$$\mu_\tau \, \Delta\tau + o(\Delta\tau) = \Pr \text{ [an individual alive at time } \tau \text{ will die in the interval } (\tau, \tau + \Delta\tau)], \text{ for } \tau \geq 0,$$

where $\Delta\tau$ stands for an infinitesimal time interval and $o(\Delta\tau)$ a quantity of smaller order of magnitude than $\Delta\tau$. It can be shown [5] that

$$p_x(t) = \exp\left\{-\int_x^{x+t} \mu_\tau \, d_\tau\right\}$$

is the probability that an individual alive at x will survive to $(x + t)$. If we assume a constant force of mortality within the interval $(x, x + 1)$, say $\mu_\tau = \mu_x$ depending only on x, for $x < \tau \leqq x + 1$, then the probability of surviving the interval is given by[5]

$$p_x = e^{-\mu_x}.$$

For the subinterval $(x, x + t)$, with t between zero and one, we have

$$p_x(t) = e^{-t\mu_x} = p_x^t, \quad \text{for} \quad 0 < t \leq 1.$$

Consider first the group of m individuals, each of whom has a constant probability p_x of surviving and a probability $q_x = 1 - p_x$ of dying in the interval $(x, x + 1)$. We have then a typical binomial case with the probability function:

$$f_1 = p_x^s(1 - p_x)^\delta. \tag{1}$$

The expected number of survivors and deaths are given, respectively, by

$$E(s \mid m) = mp_x, \quad \text{and} \quad E(\delta \mid m) = m(1 - p_x). \tag{2}$$

The distribution of the random variables in the group due for withdrawal is not so straightforward. Making the assumption that, on

[5] When the assumption of a constant force of mortality is strong for an interval where the death rate is high, one may subdivide the interval and estimate the probability for each subinterval separately.

the average, each of the m individuals will withdraw at the point $x + \frac{1}{2}$, the probability of withdrawing alive is equal to $p_x^{1/2}$, and the probability of dying before the time of withdrawal $(1 - p_x^{1/2})$. Again we have a binomial case with the probability function[6]

$$f_2 = p_x^{w/2}(1 - p_x^{1/2})^{\epsilon}. \tag{3}$$

The expected number of survivors and deaths are given, respectively, by

$$E(w \mid n) = np_x^{1/2}, \quad \text{and} \quad E(\epsilon \mid n) = n(1 - p_x^{1/2}). \tag{4}$$

Since the N_x individuals are divided at time x into two distinctly different groups according to their withdrawal status, the joint probability of all the random variables is the product of the two probability functions (1) and (3),

$$f_1 f_2 = p_x^{(s+w/2)}(1 - p_x)^{\delta}(1 - p_x^{1/2})^{\epsilon}. \tag{5}$$

1.2. *The maximum likelihood estimators and their asymptotic variances.*

We are now in a position to use the maximum likelihood principle to obtain the estimator of the probability p_x and its complement q_x, and the asymptotic variance. Taking the logarithm of the joint probability function (5), we have the likelihood function

$$L = (s + \tfrac{1}{2}w) \ln p_x + \delta \ln (1 - p_x) + \epsilon \ln (1 - p_x^{1/2}). \tag{6}$$

Differentiating (6) with respect to p_x and setting the derivative equal to zero give the likelihood equation

$$(s + \tfrac{1}{2}w)\hat{p}_x^{-1} - \delta(1 - \hat{p}_x)^{-1} - \frac{\epsilon}{2}\hat{p}_x^{-1/2}(1 - \hat{p}_x^{1/2})^{-1} = 0,$$

which implies

$$\left(N_x - \frac{n}{2}\right)\hat{p}_x + \frac{\epsilon}{2}\hat{p}_x^{1/2} - (s + \tfrac{1}{2}w) = 0, \tag{7}$$

a quadratic equation in $\hat{p}_x^{1/2}$. Since $\hat{p}_x^{1/2}$ cannot take on negative values, we have the estimators,

$$\hat{p}_x = \left[\frac{-\frac{1}{2}\epsilon + \sqrt{\frac{1}{4}\epsilon^2 + 4(N_x - \frac{1}{2}n)(s + \frac{1}{2}w)}}{2(N_x - \frac{1}{2}n)}\right]^2 \tag{8}$$

[6] A more plausible assumption perhaps is that a withdrawal takes place randomly throughout the interval. However, under this assumption the probability of withdrawing alive is

$$\int_x^{x+1} e^{-(r-x)\mu_x}\, dr = -(1 - p_x)/\ln p_x,$$

and the resulting maximum likelihood equation is too unwieldy. When the probability of survival is not too low, the above expression and $p_x^{\frac{1}{2}}$ are close to each other. For $p_x = .70$, for example, $p_x^{\frac{1}{2}} = .837$ and $-(1 - p_x)/\ln p_x = .840$. In the case of extremely high mortality, one should subdivide the interval.

and

$$\hat{q}_x = 1 - \hat{p}_x . \tag{9}$$

The maximum likelihood estimator (8) is not unbiased; however, it is consistent in the sense that when the random variables s, w, and ϵ are replaced with their respective expectations as given by (2) and (4), the resulting expression is identical with the probability p_x. That is,

$$p_x \equiv \left[\frac{-\frac{1}{2}n(1 - p_x^{\frac{1}{2}}) + \sqrt{\frac{1}{4}n^2(1 - p_x^{\frac{1}{2}})^2 + 4(N_x - \frac{1}{2}n)(mp_x + \frac{1}{2}np_x^{\frac{1}{2}})}}{2(N_x - \frac{1}{2}n)}\right]^2 .$$

To derive the formula for the asymptotic variance of the estimator $\hat{p}_x$, (or $\hat{q}_x$), we find the expectation of the second derivative of (6):

$$E\left(\frac{\partial^2 L}{\partial p_x^2}\right) = -\left[\frac{M_x}{p_x q_x} + \pi\right], \tag{10}$$

where

$$M_x = m + n(1 + p_x^{1/2})^{-1} \tag{11}$$

and

$$\pi = \frac{n}{4(1 + p_x^{1/2})^2 p_x^{3/2}}(1 - p_x^{1/2}). \tag{12}$$

According to the theorem on the asymptotic efficiency of an estimator, the asymptotic variance of $\hat{p}_x$ (or $\hat{q}_x$) is given by the negative inverse of the expectation (10),

$$\sigma_{\hat{p}_x}^2 = 1/[M_x/(p_x q_x) + \pi]. \tag{13}$$

Usually the quantity π in the denominator of (13) will be small in comparison with the preceding term, and may be neglected to give the approximate formula

$$\sigma_{\hat{p}_x}^2 = p_x q_x / M_x . \tag{14}$$

The sample variance of $\hat{p}_x$ (or $\hat{q}_x$) is obtained by substituting (8) and (9) in (13) or (14).

Remark 1: The problem discussed here relates to the study in which N_x is large. If N_x is small, one may use the exact time of death of each of the D patients and the exact time of withdrawal of each of the w patients to estimate the probability p_x. In this case, there will be N_x individual observations within the interval $(x, x + 1)$, and obviously it is unnecessary to consider the N_x patients as two distinct groups according to their withdrawal status. Let $t_i \leq 1$ be the time

of death within the interval $(x, x+1)$ of the i-th death, for $i = 1, \cdots, D$, with a probability

$$e^{-(t_i - x)\mu_x}\mu_x\, dt_i\,, \quad \text{for} \quad i = 1, \cdots, D;$$

let $T_j \leq 1$ be the time of withdrawal alive of the j-th withdrawal, for $j = 1, \cdots, w$, with a probability

$$e^{-T_j\mu_x}, \quad \text{for} \quad j = 1, \cdots, w;$$

then the joint probability function of all the N_x observations becomes

$$p_x^{s} \prod_{i=1}^{D} (e^{-(t_i - x)\mu_x}\mu_x\, dt_i) \prod_{j=1}^{w} (e^{-T_j\mu_x}) = (-\ln p_x)^D p_x^{(s + \sum_{i=1}^{D} t_i + \sum_{j=1}^{w} T_j)} \prod_{i=1}^{D} dt_i\,.$$

Maximizing the last expression with respect to p_x gives the maximum-likelihood estimator (cf. [18]),

$$\hat{p}_x = \exp\left[-D \Big/ \left(s + \sum_{i=1}^{D} t_i + \sum_{j=1}^{w} T_j\right)\right].$$

1.3. *Observed expectation of life.*

A life table for the follow-up subjects can be readily constructed, once $\hat{p}_x$ and $\hat{q}_x$ have been determined from (8) and (9) for each interval of the study period. Let an arbitrary number l_0 denote the number of patients admitted to the study. The number l_x who survive to the exact time x is computed from the formula $l_x = l_0\hat{p}_0\hat{p}_1 \cdots \hat{p}_{x-1}$, and $l_x/l_0 = \hat{p}_0\hat{p}_1 \cdots \hat{p}_{x-1}$ is the estimated x-year survival rate. For a patient alive at time x, the observed expectation of life can be expressed by the equation:

$$\hat{e}_x = a_x + c_{x+1}\hat{p}_x + c_{x+2}\hat{p}_x\hat{p}_{x+1} + \cdots + c_y\hat{p}_x\hat{p}_{x+1} \cdots \hat{p}_{y-1} + c_{y+1}\hat{p}_x\hat{p}_{x+1} \cdots \hat{p}_y + \cdots, \qquad (15)$$

where a_x is the average time lived in the interval $(x, x+1)$ by the patients who die in that interval, and $c_x = 1 - a_{x-1} + a_x$. If, in a study covering a period of y years, there are no survivors remaining from the patients who entered the study in its first year, $\hat{p}_{y-1}$ will be zero, and $\hat{e}_x$ can be computed readily from the collected data. In the typical study, however, there will be w_{y-1} survivors who entered the study in its first year and withdraw alive in the final interval $(y-1, y)$. In such cases, it is evident from (8) that $\hat{p}_{y-1}$ is greater than zero and the values of $\hat{p}_y$, $\hat{p}_{y+1}$, $\cdots$ are not observed within the limits of the study. Consequently, $\hat{e}_x$ cannot be computed from equation (15).

It is nevertheless possible to estimate $\hat{e}_x$ with a certain degree of accuracy if w_{y-1} is small. Suppose we rewrite equation (15) in the form

$$\hat{e}_x = a_x + c_{x+1}\hat{p}_x + c_{x+2}\hat{p}_x\hat{p}_{x+1} + \cdots + c_y\hat{p}_x\hat{p}_{x+1}\cdots\hat{p}_{y-1} + \frac{l_y}{l_x}(c_{y+1}\hat{p}_y + c_{y+2}\hat{p}_y\hat{p}_{y+1} + \cdots), \qquad (16)$$

where l_y/l_x is written for $\hat{p}_x\hat{p}_{x+1}\cdots\hat{p}_{y-1}$. The problem is to estimate the values of $\hat{p}_y$, $\hat{p}_{y+1}$, $\cdots$ in the last term, since the preceding terms can be computed from the data available.

As a first approach, consider a typical interval $(z, z+1)$ beyond time y with the probability of surviving the interval:

$$p_z = \exp\left(-\int_z^{z+1} \mu_\tau\, d\tau\right), \quad \text{for} \quad z = y, y+1, \cdots.$$

If the force of mortality is constant for $z \geq y$, the probability of survival is independent of z and we may write

$$p_z = e^{-\mu} = p, \quad \text{for} \quad z = y, y+1, \cdots.$$

Under this assumption $c_z = 1$, and we may replace the last term of (16) with $(l_y/l_x)(\hat{p} + \hat{p}^2 + \cdots)$, which converges to $(l_y/l_x)\hat{p}/(1-\hat{p})$. As a result, we have

$$\hat{e}_x = a_x + c_{x+1}\hat{p}_x + c_{x+2}\hat{p}_x\hat{p}_{x+1} + \cdots + c_y\hat{p}_x\hat{p}_{x+1}\cdots\hat{p}_{y-1} + \frac{l_y}{l_x}[\hat{p}/(1-\hat{p})].$$

Clearly, $\hat{p}$ may be set equal to $\hat{p}_{y-1}$ if the force of mortality is assumed to be constant beginning with time $(y-1)$ instead of time y. From the point of view of sample variation, however, it is desirable to base the estimate $\hat{p}$ on as large a sample size as possible. Suppose there exists a time T, for $T < y$, such that $\hat{p}_T$, $\hat{p}_{T+1}$, $\cdots$ are approximately equal, thus indicating a constant force of mortality after time T. Then $\hat{p}$ may be set equal to $\hat{p}_T$, and the formula for the observed expectation of life becomes (cf. [4]):

$$\hat{e}_x = a_x + c_{x+1}\hat{p}_x + c_{x+2}\hat{p}_x\hat{p}_{x+1} + \cdots + c_y\hat{p}_x\hat{p}_{x+1}\cdots\hat{p}_{y-1} + \frac{l_y}{l_x}[\hat{p}_T/(1-\hat{p}_T)], \qquad (17)$$

for $x = 0, \cdots, y-1$. When a_x is approximated with $\frac{1}{2}$, $c_x = 1$.

Although formula (17) holds for $x = 0, \cdots, y-1$, it will be apparent to the reader that the smaller the x, the larger the value of l_x,

and the smaller will be the contribution of the last term. If the ratio l_y/l_x is small, the error in assuming a constant force of mortality beyond y and in the choice of $\hat{p}_T$ will have but little effect on the value of $\mathring{e}_x$.

1.4. *The sample variance of the observed expectation of life.*

To avoid confusion in notation let us denote by α a fixed number and consider the observed expectation of life $\mathring{e}_\alpha$ as given in formula (17). It was proven in [5] that the estimated probabilities of surviving any two non-overlapping intervals have a zero covariance, and hence the sample variance of the observed expectation of life may be computed from

$$S^2_{\mathring{e}_\alpha} = \sum_{x \geq \alpha} [\partial \mathring{e}_\alpha / \partial \hat{p}_x]^2 S^2_{\hat{p}_x}, \tag{18}$$

where the derivatives are taken at the observed point $\hat{p}_x$, for $x \geq \alpha$. In the present case, we have

$$[\partial \mathring{e}_\alpha / \partial \hat{p}_x] = \hat{p}_{\alpha x}[\mathring{e}_{x+1} + (1 - a_x)], \quad \text{for} \quad x \neq T, \tag{19}$$

and

$$[\partial \mathring{e}_\alpha / \partial \hat{p}_T] = \hat{p}_{\alpha T}[\mathring{e}_{T+1} + (1 - a_T) + \{\hat{p}_{TT}/(1 - \hat{p}_T)^2\}], \text{ for } \alpha \leq T, \tag{20}$$

$$= \hat{p}_{\alpha\alpha}/(1 - \hat{p}_T)^2, \quad \text{for} \quad \alpha > T,$$

where $\hat{p}_{\alpha x} = \hat{p}_\alpha \hat{p}_{\alpha+1} \cdots \hat{p}_{x-1}$. Substituting (19) and (20) in (18) gives the sample variance of $\mathring{e}_\alpha$,

$$S^2_{\mathring{e}_\alpha} = \sum_{\substack{x=\alpha \\ x \neq T}}^{y-1} \hat{p}^2_{\alpha x}[\mathring{e}_{x+1} + (1 - a_x)]^2 S^2_{\hat{q}_x}$$

$$+ \hat{p}^2_{\alpha T}[\mathring{e}_{T+1} + (1 - a_T) + \{\hat{p}_{TT}/(1 - \hat{p}_T)^2\}]^2 S^2_{\hat{q}_T} \tag{21}$$

for $\alpha \leq T$, and

$$S^2_{\mathring{e}_\alpha} = \sum_{x=\alpha}^{y-1} \hat{p}^2_{\alpha x}[\mathring{e}_{x+1} + (1 - a_x)]^2 S^2_{\hat{q}_x}$$

$$+ \{\hat{p}^2_{\alpha\alpha}/(1 - \hat{p}_T)^4\} S^2_{\hat{q}_T}, \quad \text{for} \quad \alpha > T. \tag{21a}$$

The value of $\hat{p}_x$ and the sample variance of $\hat{q}_x$ are obtained from formulas (8) and (13), respectively. When a_x is approximated with $\frac{1}{2}$, the quantity $(1 - a_x)$ in formulas (21) and (21a) may be replaced by $\frac{1}{2}$.

PART II. CONSIDERATION OF COMPETING RISKS

2.1. *Relations between net, crude, and partial crude probabilities.*

In a follow-up study, as in general mortality analysis, one may be interested in death due to a specific cause, or to a group of causes.

Depending upon the questions to be answered, the investigator may explore three general types of probabilities of death with respect to a specific cause, or risk:

1. *The crude probability.* The probability of death from a specific cause in the presence of all other risks in a population.
2. *The net probability.* The probability of death if a specific cause were the only cause in effect in the population or, conversely, the probability of death if a specific risk were eliminated from the population.
3. *The partial crude probability.* The probability of death from a specific cause in the presence of all other risks but with a second risk eliminated from the population.

Obviously, in the human population, the net and partial crude probabilities usually cannot be estimated directly except through their relations with the crude probability. The study of such relations is part of the problem of "competing risks", or "multiple-decrement". The subject has been variously discussed in the literature (see, for example, [12], [15], and [19]) and will be reviewed here only by way of introducing notation.

Assume c risks of death (or causes) acting simultaneously on each individual of a population (that is, competing for the life of the individual), and let these risks be denoted by $R_1, \cdots, R_c$. For each risk there is a corresponding force of mortality, $\nu_{\tau 1}, \cdots, \nu_{\tau c}$, each of which is a function of time τ, and the sum of these

$$\nu_{\tau 1} + \cdots + \nu_{\tau c} = \mu_\tau \tag{22}$$

is then the total force of mortality. Within the time interval $(x, x+1)$, we shall assume a constant force of mortality for each risk, say $\nu_{\tau k} = \nu_{xk}$, depending only on x and k, for $x < \tau \leq x+1$. For all risks, we have $\mu_\tau = \mu_x$, for $x < \tau \leq x+1$.

Let $Q_{xk}(t)$ be the crude probability that an individual alive at time x will die in the interval $(x, x+t)$, for $0 < t \leq 1$, from cause R_k in the presence of all other risks. It follows directly from addition and multiplication theorems that

$$Q_{xk}(t) = \int_x^{x+t} e^{-(\tau - x)\mu_x} \nu_{xk}\, d\tau, \quad \text{for} \quad 0 < t \leq 1; \qquad k = 1, \cdots, c. \tag{23}$$

The first factor of the integrand is the probability of surviving from x to τ when all risks of death are acting, while the second factor is

the instantaneous probability of death from cause R_k. Integrating (23) gives

$$Q_{xk}(t) = \frac{\nu_{xk}}{\mu_x}[1 - e^{-t\mu_x}] = \frac{\nu_{xk}}{\mu_x}[1 - p_x(t)],$$

$$\text{for } 0 < t \leq 1; \quad k = 1, \cdots, c. \tag{24}$$

It is clear from (22) that the sum of the crude probabilities in (24) is equal to the complement of $p_x(t)$, or

$$Q_{x1}(t) + \cdots + Q_{xc}(t) + p_x(t) = 1, \quad \text{for } 0 < t \leq 1. \tag{25}$$

For $t = 1$, we shall abbreviate $Q_{xk}(1)$ to Q_{xk}, etc. For the purpose of this study we are particularly interested in the subinterval $(x, x + \frac{1}{2})$, with

$$Q_{xk}(\tfrac{1}{2}) = \frac{\nu_{xk}}{\mu_x}[1 - e^{-\mu_x/2}] = Q_{xk}[1 + p_x^{1/2}]^{-1}, \quad \text{for } k = 1, \cdots, c. \tag{26}$$

In this case the sum of the crude probabilities (26) is the complement of $p_x^{1/2}$, the probability of surviving half the interval, and

$$Q_{x1}[1 + p_x^{1/2}]^{-1} + \cdots + Q_{xc}[1 + p_x^{1/2}]^{-1} + p_x^{1/2} = 1. \tag{27}$$

When risk R_k acts alone, the net probability that an individual alive at time x will die in the interval $(x, x + 1)$ is

$$q_{xk} = 1 - e^{-\nu_{xk}} = 1 - [e^{-\mu_x}]^{\nu_{xk}/\mu_x}. \tag{28}$$

From formulas (24) and (28) we obtain the relation between the net and crude probabilities

$$q_{xk} = 1 - p_x^{Q_{xk}/q_x}, \quad \text{for } k = 1, \cdots, c. \tag{29}$$

By analogy we can write the net probability of death in the interval $(x, x + 1)$ when risk R_k is eliminated,

$$q_{x.k} = 1 - p_x^{(q_x - Q_{xk})/q_x}, \quad \text{for } k = 1, \cdots, c. \tag{30}$$

Now suppose that R_1 is eliminated as a cause of death, and let $Q_{xk.1}$ be the partial crude probability that an individual alive at time x will die in the interval $(x, x + 1)$ from cause R_k in the presence of all other risks, for $k = 2, \cdots, c$. Using a similar reasoning as in the crude probability [eq. (23)], we can write

$$Q_{xk.1} = \int_x^{x+1} e^{-(\tau - x)(\mu_x - \nu_{x1})} \nu_{xk}\, d\tau$$

$$= \frac{Q_{xk}}{q_x - Q_{x1}}[1 - p_x^{(q_x - Q_{x1})/q_x}], \quad \text{for } k = 2, \cdots, c. \tag{31}$$

Similarly, if risks R_1 and R_2 are eliminated, the partial crude probability that an individual alive at x will die in the interval $(x, x+1)$ from cause R_k in the presence of all other causes is given by

$$Q_{xk\,12} = \frac{Q_{xk}}{q_x - Q_{x1} - Q_{x2}} [1 - p_x^{(q_x - Q_{x1} - Q_{x2})/q_x}], \text{ for } k = 3, \cdots, c. \quad (32)$$

A detailed discussion on the partial crude probabilities is given in [7].

2.2. *The basic random variables and their joint probability function.*

The identification of the random variables in a follow-up study in the presence of competing risks and the derivation of their joint probability function follows directly from the discussion in Section 1 of Part I. The deaths in each of the two groups according to withdrawal status are further divided by cause of death as shown in Table 1, Part I.

Each of the m individuals not due for withdrawal in the interval $(x, x+1)$ will fall into one of the $c+1$ mutually exclusive groups, depending upon whether he survives the interval or dies from cause $R_1, \cdots, R_c$, with the sum of the corresponding probabilities $p_x, Q_{x1}, \cdots, Q_{xc}$, equal to unity [eq. (25)]. Thus we have a multinomial case with the probability function

$$f_1 = p_x^s Q_{x1}^{\delta_1} \cdots Q_{xc}^{\delta_c}, \quad (33)$$

where s is the number of survivors and δ_k is the number of deaths from cause R_k, for $k = 1, \cdots, c$. Their mathematical expectations are given respectively, by

$$E(s \mid m) = mp_x, \text{ and } E(\delta_k \mid m) = mQ_{xk}, \text{ for } k = 1, \cdots, c. \quad (34)$$

Each individual in the group of n due for withdrawal in the interval $(x, x+1)$ has the probability $p_x^{1/2}$ of withdrawing alive and the probability

$$Q_{xk}(\tfrac{1}{2}) = Q_{xk}(1 + p_x^{1/2})^{-1}, \text{ for } k = 1, \cdots, c, \quad (26)$$

of dying from cause R_k. Since $p_x^{1/2}$ and the probabilities in (26) again add up to unity [eq. (27)], the n observations also constitute a multinomial case with the probability function (cf. footnote 6)

$$f_2 = p_x^{w/2} \prod_{k=1}^{c} [Q_{xk}(1 + p_x^{1/2})^{-1}]^{\epsilon_k}, \quad (35)$$

where w is the number of individuals withdrawing alive and ϵ_k the number of individuals who die from cause R_k before the time of withdrawal. The mathematical expectations are, respectively,

$$E(w \mid n) = np_x^{1/2}, \text{ and } E(\epsilon_k \mid n) = nQ_{xk}(1 + p_x^{1/2})^{-1},$$
$$\text{for } k = 1, \cdots, c. \quad (36)$$

Because of the separation of the individuals into two distinct groups at time x according to their withdrawal status, the joint probability of all the random variables in Table 1 is the product of the two joint probabilities (33) and (35):

$$f_1 f_2 = p_x^{s+w/2} \prod_{k=1}^{c} Q_{xk}^{d_k} \prod_{k=1}^{c} [Q_{xk}(1 + p_x^{1/2})^{-1}]^{\epsilon_k}. \tag{37}$$

Formula (37) may be simplified by rearranging terms and using the relations, $D_k = \delta_k + \epsilon_k$, and $\epsilon = \epsilon_1 + \cdots + \epsilon_c$, to give the final form of the joint probability function

$$f_1 f_2 = p_x^{s+w/2}(1 + p_x^{1/2})^{-\epsilon} \prod_{k=1}^{c} Q_{xk}^{D_k}. \tag{38}$$

2.3. *Maximum-likelihood estimators of crude, net, and partial crude probabilities.*

We will again use the maximum likelihood principle to obtain the estimators of the probabilities: p_x, Q_{x1}, $\cdots$, Q_{xc}. In this case the likelihood function obtained from (38) is

$$L = (s + \tfrac{1}{2}w) \ln p_x - \epsilon \ln (1 + p_x^{1/2}) + D_1 \ln \left(1 - p_x - \sum_{k=2}^{c} Q_{xk}\right) + \sum_{k=2}^{c} D_k \ln Q_{xk}, \tag{39}$$

where the substitution

$$Q_{x1} = 1 - p_x - \sum_{k=2}^{c} Q_{xk} \tag{40}$$

has been made. Differentiating the likelihood function (39) with respect to p_x, Q_{x2}, $\cdots$, Q_{xc}, respectively, and setting the derivatives equal to zero, we obtain a system of c simultaneous equations:

$$\partial L/\partial p_x = [(s + \tfrac{1}{2}w)/\hat{p}_x] - \epsilon/[2\hat{p}_x^{1/2}(1 + \hat{p}_x^{1/2})] - (D_1/\hat{Q}_{x1}) = 0, \tag{41a}$$

$$\partial L/\partial Q_{xk} = (D_k/\hat{Q}_{xk}) - (D_1/\hat{Q}_{x1}) = 0, \quad \text{for} \quad k = 2, \cdots, c. \tag{41b}$$

From (41b) it can be deduced that

$$D_k/\hat{Q}_{xk} = D/(1 - \hat{p}_x), \quad \text{for} \quad k = 1, \cdots, c, \tag{42}$$

and therefore the ratio $D_1/\hat{Q}_{x1}$ in equation (41a) can be replaced with $D/(1 - \hat{p}_x)$. When this substitution is made and the terms in (41a) are rearranged we have a quadratic equation in $\hat{p}_x^{1/2}$ that is identical to equation (7) in Part I. Hence the estimators $\hat{p}_x$, in (8), and $\hat{q}_x$ for all causes of death will have the same value as in the simple case where death is investigated without specification to cause, as one would anticipate. Substituting (8) in (42) gives the estimators

$$\hat{Q}_{xk} = (D_k/D)\hat{q}_x , \quad \text{for} \quad k = 1, \cdots, c. \tag{43}$$

To obtain the estimators of the net and partial crude probabilities, we substitute (43) in formula (29), (30), (31), and (32), and after simplification,

$$\hat{q}_{xk} = 1 - \hat{p}_x^{D_k/D}, \quad \text{for} \quad k = 1, \cdots, c; \tag{44}$$

$$\hat{q}_{x.k} = 1 - \hat{p}_x^{(D-D_k)/D}, \quad \text{for} \quad k = 1, \cdots, c; \tag{45}$$

$$\hat{Q}_{xk.1} = [D_k/(D - D_1)][1 - \hat{p}_x^{(D-D_1)/D}], \quad \text{for} \quad k = 2, \cdots, c; \tag{46}$$

and

$$\hat{Q}_{xk.12} = [D_k/(D - D_1 - D_2)][1 - \hat{p}_x^{(D-D_1-D_2)/D}], \text{ for } k = 3, \cdots, c. \tag{47}$$

The estimators given in formulas (44), (45), (46), and (47) are also maximum likelihood estimators because of the invariance property of maximum likelihood estimators.

Remark 2: If there were no withdrawals in the interval $(x, x + 1)$, i.e., if $n = 0$, the problem is reduced to the classical multiple-decrement problem, with s survivors and $D_k = \delta_k$ deaths from cause R_k, for $k = 1, \cdots, c$. These random variables will still have a multinomial distribution [eq. (33)], and the formulas for the estimators of p_x, q_x, and Q_{xk} are reduced to

$$\hat{p}_x = s/N_x , \tag{8a}$$

$$\hat{q}_x = D/N_x , \tag{9a}$$

and

$$\hat{Q}_{xk} = D_k/N_x , \quad \text{for} \quad k = 1, \cdots, c. \tag{43a}$$

Formulas (44) through (47) may still be used for the estimators of the net and partial crude probabilities, but with $\hat{p}_x$ given by (8a).

Remark 3: The problem of cases lost to the study due to failure of follow-up is still unsolved, and perhaps it has no unique solution. Since the probability that a patient will be lost to follow-up is in part dependent upon the type of a study, assumptions with respect to lost cases may be valid for one study but not for another. If the number of lost cases is small, depending upon the type of study, one of the following assumptions may be made and the data handled accordingly: (1) patients lost will have the same probability of surviving as patients not lost, and may be deleted from the study; (2) all lost cases survive to the close of the study; (3) all die at the time of becoming lost; and (4) becoming lost is another competing risk. If sufficient knowledge of follow-up is unavailable, the fourth alternative is preferred.

2.4. *Asymptotic variance and covariance of the estimators.*

Formulas for the variance and covariance of the estimators may be determined by using the asymptotic property of maximum-likelihood estimators. The inverse of the asymptotic covariance matrix of the estimators, $\hat{p}_x$, $\hat{Q}_{x2}$, $\cdots$, $\hat{Q}_{xc}$, is given by

$$\| \Lambda \| = \begin{bmatrix} \left\| -E\left(\frac{\partial^2 L}{\partial p_x^2}\right) \right\| & \left\| -E\left(\frac{\partial^2 L}{\partial p_x \, \partial Q_{xk}}\right) \right\| \\ 1 \times 1 & 1 \times (c-1) \\ \hline \left\| -E\left(\frac{\partial^2 L}{\partial p_x \, \partial Q_{xk}}\right) \right\|' & \left\| -E\left(\frac{\partial^2 L}{\partial Q_{xh} \, \partial Q_{xk}}\right) \right\| \\ (c-1) \times 1 & (c-1) \times (c-1) \end{bmatrix} \tag{48}$$

in which the elements are obtained by differentiating formula (41a) and (41b). Direct calculation gives the following mathematical expectations

$$-E(\partial^2 L/\partial p_x^2) = M_x[(1/p_x) + (1/Q_{x1})] + \pi, \tag{49}$$

$$-E(\partial^2 L/\partial p_x \, \partial Q_{xk}) = M_x/Q_{x1} \, , \quad \text{for} \quad k = 2, \cdots, c, \tag{50}$$

$$-E(\partial^2 L/\partial Q_{xh} \, \partial Q_{xk}) = M_x/Q_{x1} \, , \quad \text{for} \quad h \neq k; h, k = 2, \cdots, c, \tag{51}$$

and

$$-E(\partial^2 L/\partial Q_{xk}^2) = M_x[(1/Q_{x1}) + (1/Q_{xk})], \quad \text{for} \quad k = 2, \cdots, c, \tag{52}$$

where M_x and π are defined by equation (11) and (12), respectively, of Part I. Substituting the respective expectations into (48), we have

$$\| \Lambda \| = \begin{bmatrix} M_x\left(\frac{1}{p_x}+\frac{1}{Q_{x1}}\right)+\pi & M_x/Q_{x1} & M_x/Q_{x1} & \cdots & M_x/Q_{x1} \\ \hline M_x/Q_{x1} & M_x\left(\frac{1}{Q_{x1}}+\frac{1}{Q_{x2}}\right) & M_x/Q_{x1} & \cdots & M_x/Q_{x1} \\ M_x/Q_{x1} & M_x/Q_{x1} & M_x\left(\frac{1}{Q_{x1}}+\frac{1}{Q_{x3}}\right) & \cdots & M_x/Q_{x1} \\ \vdots & \vdots & \vdots & & \vdots \\ M_x/Q_{x1} & M_x/Q_{x1} & M_x/Q_{x1} & \cdots & M_x\left(\frac{1}{Q_{x1}}+\frac{1}{Q_{xc}}\right) \end{bmatrix}$$

with its determinant

$$\Lambda = (M_x^c/Q_{x1} \cdots Q_{xc}p_x) + \pi(M_x^{c-1}/Q_{x1} \cdots Q_{xc})(1 - p_x). \quad (54)$$

Denoting the cofactors of the determinant by Λ_{hk}, for $h, k = 1, \cdots, c$, the formulas for the asymptotic variance and covariance are given by

$$\sigma^2_{\hat{p}_x} = \Lambda_{11}/\Lambda = (p_xq_x/M_x)[1/\{1 + (\pi p_xq_x/M_x)\}], \quad (55)$$

$$\sigma^2_{\hat{Q}_{xk}} = \Lambda_{kk}/\Lambda = [Q_{xk}(1 - Q_{xk})/M_x]\left[\frac{1 + \{\pi p_x(q_x - Q_{xk})/M_x(1 - Q_{xk})\}}{1 + \{\pi p_xq_x/M_x\}}\right],$$

$$\text{for} \quad k = 2, \cdots, c, \quad (56)$$

$$\sigma^2_{\hat{p}_x,\hat{Q}_{xk}} = \Lambda_{1k}/\Lambda = -(p_xQ_{xk}/M_x)[1/\{1 + (\pi p_xq_x/M_x)\}],$$

$$\text{for} \quad k = 2, \cdots, c, \quad (57)$$

and

$$\sigma^2_{\hat{Q}_{xh},\hat{Q}_{xk}} = \Lambda_{xk}/\Lambda = -(Q_{xh}Q_{xk}/M_x)[\{1 + (\pi p_x/M_x)\}/\{1 + (\pi p_xq_x/M_x)\}],$$

$$\text{for} \quad h \neq k; \qquad h, k = 2, 3, \cdots, c. \quad (58)$$

Since the term Q_{x1} was not explicitly included in the likelihood function (39), the formulas for the variance of $\hat{Q}_{x1}$ and the covariances between $\hat{Q}_{x1}$ and other estimators were not presented. It is obvious by reason of symmetry, however, that expressions for $\hat{Q}_{xk}$ do start from $\hat{Q}_{x1}$, which is to say that formulas (56), (57), and (58) hold also for $k = 1$.

The quantities inside the square brackets in formulas (55) through (58) may be approximated with unity when M_x is moderately large. These formulas then reduce to familiar expressions of the multinomial case:

$$\sigma^2_{\hat{p}_x} = p_xq_x/M_x, \quad (59)$$

$$\sigma^2_{\hat{Q}_{xk}} = Q_{xk}(1 - Q_{xk})/M_x, \quad \text{for} \quad k = 1, \cdots, c, \quad (60)$$

$$\sigma_{\hat{p}_x,\hat{Q}_{xk}} = -p_xQ_{xk}/M_x, \quad \text{for} \quad k = 1, \cdots, c, \quad (61)$$

and

$$\sigma_{\hat{Q}_{xh},\hat{Q}_{xk}} = -Q_{xh}Q_{xk}/M_x, \quad \text{for} \quad h \neq k; \qquad h, k = 1, 2, \cdots, c. \quad (62)$$

Formulas for the asymptotic variance and covariance of the estimators of the net and partial crude probabilities can be obtained with the same approach as employed in [7]. To save space, only two formulas are presented below.

$$\sigma^2_{\hat{q}_{x:k}} = [(1 - q_{x:k})^2/M_xp_xq_x]$$

$$\cdot[p_x \ln (1 - q_{xk}) \ln (1 - q_{x:k}) + (q_x - [illegible])^2]. \quad (63)$$

for $k = 1, \cdots, c$, for the net probability of death when risk R_k is eliminated, and

$$\sigma^2_{\hat{Q}_{xk\cdot 1}} = [(q_x - Q_{x1} - Q_{xk})/\{M_x(q_x - Q_{x1})Q_{xk}\}]Q^2_{xk\cdot 1} + [\{Q_{xk\cdot 1}(q_x - Q_{x1}) - Q_{xk}\}^2/\{M_x p_x q_x(q_x - Q_{x1})\}] \cdot[(q_x - Q_{x1}) + Q_{x1}p_x(\ln p_x/q_x)^2], \quad (64)$$

for $k = 2, \cdots, c$, for the partial crude probability.

AN EXAMPLE OF LIFE TABLE CONSTRUCTION FOR THE FOLLOW-UP POPULATION

The application of the methods developed in Parts I and II will be illustrated with data collected by the Tumor Registry of the California State Department of Public Health. The material selected consists of 5982 patients[7] admitted to certain California hospitals and clinics between January 1, 1942, and December 31, 1954, with a diagnosis of cancer of the cervix uteri. For the purpose of this illustration, the latter date is taken as the common closing date of the study; the date of entrance to follow-up for each patient is the date of hospital admission.

The first step is to construct a table similar to Table 2, showing the survival experience of the patients grouped according to their withdrawal status. The interval length selected (column 1) will depend upon the nature of the investigation; in this case a fixed length of one year was convenient and satisfactory. The total number of patients admitted to the study is entered as N_0 in the first line of column 2, which in this example is 5982. To determine their withdrawal status in the first interval (0, 1) the patients were separated into two groups: admissions before 1954, and consequently at least one year before the close of the study; and admissions during the year 1954, all due for withdrawal since the study was terminated before their first anniversary. Of the patients admitted prior to 1954, s_0 (4030 in column 3) survived to their first anniversary and δ_0 (1287) died during the first year. The deaths were further divided by cause into δ_{01} (1105) deaths due to cancer of the cervix uteri and δ_{02} (182) deaths from all other causes. The survival status of the 1954 admissions is determined at the close of the study, as it is for patients due for withdrawal in any interval. In this study, w_0 (576) patients withdrew alive in the first interval, and ϵ_0 (89) patients died before the closing date. These deaths were again divided by cause into ϵ_{01} (70, column 9) and ϵ_{02} (19, column 10).

TABLE 2

[7] An additional 251 cases of uncertain survival status were deleted from this illustration.

TABLE 2

SURVIVAL EXPERIENCE FOLLOWING DIAGNOSIS OF CANCER OF THE CERVIX UTERI: CASES INITIALLY DIAGNOSED 1942–1954

Interval since diagnosis (years)	Number living at beginning of interval $(x, x+1)$	Number not due for withdrawal in interval $(x, x+1)$*				Number due for withdrawal in interval $(x, x+1)$**			
		Number surviving the interval	Number dying in the interval			Number living at time of withdrawal	Number dying before withdrawal		
			Total	Cancer of the cervix	Other causes		Total	Cancer of the cervix	Other causes
$x - x+1$	N_x	s_x	ϕ_x	δ_{x1}	δ_{x2}	w_x	ϵ_x	ϵ_{x1}	ϵ_{x2}
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
0–1	5982	4030	1287	1105	182	576	89	70	19
1–2	4030	2845	644	557	87	501	40	31	9
2–3	2845	2117	250	206	44	459	19	15	4
3–4	2117	1573	151	113	38	379	14	8	6
4–5	1573	1176	87	61	26	306	4	2	2
5–6	1176	861	57	24	33	254	4	3	1
6–7	861	660	32	16	16	167	2	2	0
7–8	660	474	22	11	11	161	3	2	1
8–9	474	344	12	5	7	116	2	1	1
9–10	344	245	11	7	4	85	3	2	1
10–11	245	158	6	4	2	78	3	1	2
11–12	158	72	4	1	3	80	2	1	1
12–13	72	0	0	0	0	72	0	0	0

*Patients admitted more than $x + 1$ years prior to closing date.
**Patients admitted between x and $x + 1$ years prior to closing date.
Source: California Tumor Registry, Department of Public Health, State of California

TABLE 3

SURVIVAL EXPERIENCE AFTER DIAGNOSIS OF CANCER OF THE CERVIX UTERI: THE MAIN LIFE TABLE FUNCTIONS AND THEIR STANDARD ERRORS

Interval since diagnosis (years)	x-year survival rate $\hat{p}_{0x}$		Estimated probability of death in interval $(x, x+1)$		Observed expectation of life at x	
$x - x+1$	1000 $\hat{p}_{0x}$	1000 $S_{\hat{p}_{0x}}$	1000 $\hat{q}_x$	1000 $S_{\hat{q}_x}$	$\mathring{e}_x$	$S_{\mathring{e}_x}$
(1)	(2)	(3)	(4)	(5)	(6)	(7)
0–1	1000.00	0.00	242.54	5.69	12.90	2.83
1–2	757.46	5.80	181.43	6.26	15.86	3.74
2–3	620.03	6.65	103.03	5.95	18.27	4.57
3–4	556.15	7.01	85.76	6.38	19.31	5.09
4–5	508.46	7.33	64.13	6.50	20.08	5.56
5–6	475.85	7.61	58.20	7.23	20.42	5.94
6–7	448.15	7.95	43.76	7.34	20.65	6.31
7–8	428.54	8.29	43.20	8.45	20.57	6.60
8–9	410.03	8.71	33.69	8.85	20.48	6.89
9–10	396.22	9.17	46.55	12.15	20.17	7.13
10–11	377.77	9.98	43.85	14.30	20.13	7.47
11–12	361.21	10.97	51.06	20.30	20.03	7.81
12–13	342.77	12.73	00.00	00.00	20.08	7.79
13	342.77	12.73	—	—	19.08	7.79

Source: California Tumor Registry, Department of Public Health, State of California.

The second interval began with the 4030 survivors from the first interval, which is entered as N_1 in line 2 of column 2. All 1953 admissions included in N_1 were due for withdrawal in the second interval.

The main life table functions and the corresponding sample standard errors as shown in Table 3 are determined from the data given in Table 2. The x-year survival rate $\hat{p}_{0x}$ is by definition equal to l_x divided by the radix l_0, or $\hat{p}_0\hat{p}_1 \cdot \cdots, \hat{p}_{x-1}$. The sample variance of $\hat{p}_{0x}$ is computed from a formula given in a previous publication [6] (see also [13]):

$$S^2_{\hat{p}_{0x}} = \hat{p}^2_{0x} \sum_{u=0}^{x-1} \hat{p}_u^{-2} S^2_{\hat{q}_u} .$$

Formulas (13) and (14) were both used to compute the sample standard error of $\hat{q}_x$, with numerical results that were almost identical to the fourth decimal place. The figures appearing in column 5 of Table 3 were obtained by formula (14). The observed expectation of life was determined from formula (17), for which $\hat{p}_T$ was set equal to $\hat{p}_{11}$.

TABLE 4

SURVIVAL EXPERIENCE AFTER DIAGNOSIS OF CANCER OF THE CERVIX UTERI: ESTIMATED CRUDE AND NET PROBABILITIES OF DEATH FROM CANCER OF THE CERVIX UTERI AND FROM OTHER CAUSES

Interval since diagnosis (years)	Estimated probability of surviving interval $(x, x+1)$	Estimated crude probabilities of death in interval $(x, x+1)$ from		Estimated net probabilities of death in interval $(x, x+1)$ when	
		Cervix cancer	Other causes	Cervix cancer Acting alone	Cervix cancer Eliminated
$x-x+1$	1000 $\hat{p}_x$	1000 $\hat{Q}_{x1}$	1000 $\hat{Q}_{x2}$	1000 q_{x1}	1000 q_{x2}
(1)	(2)	(3)	(4)	(5)	(6)
0–1	757.46	207.11	35.43	211.17	39.77
1–2	818.57	155.97	25.46	158.11	27.71
2–3	896.97	84.65	18.38	85.46	19.22
3–4	914.24	62.89	22.87	63.63	23.63
4–5	835.87	44.40	19.73	44.85	20.19
5–6	941.80	25.76	32.44	26.19	32.87
6–7	956.24	23.17	20.59	23.41	20.84
7–8	956.80	22.47	20.73	22.70	20.97
8–9	966.31	14.44	19.25	14.58	19.39
9–10	953.45	29.93	16.62	30.18	16.88
10–11	956.15	24.36	19.49	24.60	19.73
11–12	948.94	17.02	34.04	17.32	34.34
12–13	1000.00	—	—	—	—

Source: California Tumor Registry, Department of Public Health, State of California.

Table 4 shows the estimated probability of surviving each interval and the estimated crude and net probabilities of death from R_1, cancer of the cervix uteri and R_2, all other causes of death. Since only two risks are studied, the probability q_{x2} is equal to $q_{x.1}$, the net probability of death when cancer of the cervix uteri is eliminated as a risk of death from the population. For each interval the sum of $\hat{p}_x$, $\hat{Q}_{x1}$, and $\hat{Q}_{x2}$ is unity, and the estimated net probability $\hat{Q}_{xk}$ is always greater than the corresponding crude probability $\hat{Q}_{xk}$.

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THE SPEARMAN ESTIMATOR FOR SERIAL DILUTION ASSAYS[1]

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SUMMARY

A new estimation procedure is presented for the estimation of the density of organisms in a suspension by a serial dilution assay. The point estimator is based on the Spearman technique, is simply and quickly computed without special tables, and has efficiency 88 percent.

1. INTRODUCTION

To estimate the density of a specific organism in a suspension, a common method is to form a series of dilutions of the original suspension. Then from each dilution a specified volume, hereafter referred to as a dose, is placed in each of several tubes. Later the tubes are examined for evidence of growth of the organism.

Suppose $k + 1$ dilutions are used with concentrations of $z_i = a^{-i}z_0$, $i = 0, +1, +2, \cdots, +k$. z_0 is the highest concentration of original suspension used and $a > 1$ is the dilution factor.

The following notation will be used:

$x = \ln z$,
n = the number of tubes receiving a unit volume (dose) for each dilution,
r_i = the number of tubes showing signs of growth at dilution z_i,
$p_i = r_i/n$, $q_i = n - r_i$, $q_i = 1 - p_i$.

The usual model specifies a density of organisms of θ per unit volume in the original suspension and a Poisson distribution of organisms in the individual doses. Thus the probability of signs of growth (i.e., the probability of one or more organisms) in a tube receiving a dose at concentration z_i is

$$P(z_i) = 1 - e^{-\theta z_i}. \tag{1}$$

The maximum likelihood estimator (frequently called "most probable number") has been proposed [5] for estimating θ. Computational

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procedures and tables have been published to eliminate the tedious computations involved [1, 4, 7]. Cochran [2] has given some guides for designing serial dilution assays using the most probable number.

Fisher [5] proposed another estimator for θ. Computation is tedious for this estimator also. Tables have been published [6] for some of the common experimental designs.

2. POINT AND INTERVAL ESTIMATION PROCEDURES

The dose levels on the log scale, $x = \ln z$, are spaced $d = \ln a$ units apart. The probability of a growth response at dose level x is

$$F(x) = 1 - e^{-\theta e^x}. \tag{2}$$

The equidistant spacing and the "dose-response" function $F(x)$ with the characteristics of a distribution function (increasing from 0 to 1 with x) are typical of the common bioassay problem in which the object is to estimate the median (L.D. 50) or mean (μ) or $F(x)$. For such situations, Spearman [9] proposed the following estimator for μ:

$$\hat{\mu} = x_0 + \frac{d}{2} - d \sum p_i , \tag{3}$$

where $x_0 = \ln z_0$, $d = \ln a$, the summation is from $i = 0$ to $i = k$, and p_i is the proportion of tubes showing growth at dilution z_i . $F(x)$ has mean:

$$\begin{aligned} \mu &= \int_{-\infty}^{\infty} x\theta e^x e^{-\theta e^x} \, dx \\ &= \int_0^{\infty} (\ln y - \ln \theta) e^{-y} \, dy, \\ &= -\gamma - \ln \theta, \end{aligned}$$

where $\gamma = .57722$ is Euler's constant [8]. The parameter of interest θ can then be written:

$$\theta = e^{-\gamma} e^{-\mu} \tag{4}$$

and the point estimator $\hat{\theta}$ of θ based on $\hat{\mu}$ is[3]

$$\hat{\theta} = e^{-\gamma} e^{-\hat{\mu}} = e^{-\gamma - x_0 - d/2 + d\sum p_i}. \tag{5}$$

The point estimator of the number of organisms per z_0 volume is

$$z_0 \hat{\theta} = e^{-\gamma - d/2 + d\sum p_i}. \tag{6}$$

[3]The point estimator $\hat{\theta}$ is biased. Its bias is discussed in Section 4 and a correction factor is given.

For convenience, the necessity of a logarithm table can be circumvented by constructing a graph of $z_0\hat{\theta}$ as a function of $\sum p_i$, for commonly used values of a. Such a graph has been constructed (Graph 1) and its use is illustrated in the example in Section 6.

If an interval estimate of θ is desired, the interval estimate of μ is computed first and then the end points transformed by equation (5). The interval estimator of μ (confidence coefficient of .95) is given in expression (7). The justification is presented in Section 3.

$$\hat{\mu} - 1.96\sqrt{\frac{d \ln 2}{n}} < \mu < \hat{\mu} + 1.96\sqrt{\frac{d \ln 2}{n}}. \tag{7}$$

The corresponding interval estimator (C.C. = .95) for θ is

$$\hat{\theta} \exp\left(-1.96\sqrt{\frac{d \ln 2}{n}}\right) < \theta < \hat{\theta} \exp\left(1.96\sqrt{\frac{d \ln 2}{n}}\right), \tag{8}$$

where $\hat{\theta}$ is given in equation (5).

3. CHARACTERISTICS OF $\hat{\mu}$

First the values of d, n and x_0 will be assumed fixed. Then the case of x_0 randomly chosen will be discussed. In all cases it is assumed that the dose levels $x_i = \ln z_i$ span an interval wide enough so that $F(x_0) \geq .99$ and $F(x_0 - kd) \leq .01$.

The following notation will be used to differentiate between discussions with x_0 fixed and discussions with x_0 random:

- E_p denotes expectation with respect to the random variables p_i for fixed x_0.
- E_{x_0} denotes expectation with respect to the distribution of x_0 when x_0 is randomly chosen.
- E denotes expectation with respect to both x_0 and the random variables p_i.

It follows from (2) and (3) that the expected value of $\hat{\mu}$ for fixed x_0 is

$$E_p(\hat{\mu} \mid x_0) = x_0 + \frac{d}{2} - d \sum F(x_i)$$

$$= x_0 + \frac{d}{2} - d \sum (1 - \exp[-\theta e^{x_0 - id}]). \tag{9}$$

Using (4) and (9), the bias of $\hat{\mu}$ for fixed x_0, $B(\hat{\mu} \mid x_0)$, is

$$B(\hat{\mu} \mid x_0) = E_p(\hat{\mu} \mid x_0) - \mu$$

$$= x_0 + \frac{d}{2} - d \sum (1 - \exp[-\theta e^{x_0 - id}]) + \gamma + \ln \theta. \tag{10}$$

$B(\hat{\mu} \mid x_0)$ does not depend on n. It does depend on d and on x_0. For a given value of d, the bias will have a maximum and a minimum over all possible positions of x_0, subject to the conditions that $F(x_0) \geq .99$ and $F(x_0 - kd) \leq .01$. Let $B(\hat{\mu} \mid x_0)$ be differentiated with respect to x_0:

$$\frac{d}{dx_0}[B(\hat{\mu} \mid x_0)] = 1 - d \sum \theta \exp(x_0 - id) \exp(-\theta e^{x_0 - id}). \tag{11}$$

For a given d, if enough terms are carried to cover the desired range, it can be shown that (11) has two zeros with respect to x_0 on every interval of length d. These solutions yield the maximum and minimum values of the bias over all positions x_0 for fixed d. Some results, obtained numerically, are:

$$\begin{aligned} a &= 4, \quad d = \ln 4: \quad |B(\hat{\mu} \mid x_0)| \leqq .0019, \\ a &= 10, \quad d = \ln 10: \quad |B(\hat{\mu} \mid x_0)| \leqq .0417. \end{aligned} \tag{12}$$

Using (2) and (3), the variance of $\hat{\mu}$ for fixed x_0, $V(\hat{\mu} \mid x_0)$, can be written

$$V(\hat{\mu} \mid x_0) = \frac{d^2}{n} \sum F(x_i)[1 - F(x_i)]. \tag{13}$$

The sum in (13) can be approximated by the following integral. The approximation will be good if d is small and the range of dose levels x_i is large.

$$V(\hat{\mu} \mid x_0) \doteq \frac{d}{n} \int_{-\infty}^{\infty} F(x)[1 - F(x)]\, dx = \frac{d \ln 2}{n}. \tag{14}$$

For a given value of d, $V(\hat{\mu} \mid x_0)$ will depend on the position of x_0. The maximum values of $V(\hat{\mu} \mid x_0)$ can be obtained for given d by differentiating (13):

$$\frac{d}{dx_0}[V(\hat{\mu} \mid x_0)]$$

$$= \frac{d^2}{n} \sum \theta e^{x_0 - id} \exp(-\theta e^{x_0 - id})[2 \exp(-\theta e^{x_0 - id}) - 1]. \tag{15}$$

Zeros for (15) can be obtained numerically for any given d, using a range of doses large enough so that terms ignored in (15) are negligible. The values of x_0 thus obtained can be substituted in (13) to obtain the maximum and minimum variance. The results below are presented relative to the approximate variance (14):

$$a = 4, \qquad d = \ln 4: \qquad \left| \frac{V(\hat{\mu} \mid x_0) - \frac{d \ln 2}{n}}{\frac{d \ln 2}{n}} \right| \leqq .0056,$$

$$a = 10, \qquad d = \ln 10: \qquad \left| \frac{V(\hat{\mu} \mid x_0) - \frac{d \ln 2}{n}}{\frac{d \ln 2}{n}} \right| \leqq .0977. \tag{16}$$

The numerical results (12) and (16) indicate that, if the range of doses is wide enough and the dilution factor a is 10 or less, then the following approximations can be used regardless of the position of x_0 :

$$E_p(\hat{\mu} \mid x_0) \doteq \mu, \qquad V(\hat{\mu} \mid x_0) \doteq \frac{d \ln 2}{n}. \tag{17}$$

Suppose that x_0 is randomly chosen with uniform density over an interval of length d, say $(A, A + d)$. Then the expectation of μ can be taken with respect to x_0 and the p_i :

$$\begin{aligned} E(\hat{\mu}) = E_{x_0}[E_p(\hat{\mu} \mid x_0)] &= \frac{1}{d} \int_A^{A+d} E_p(\hat{\mu} \mid x_0)\, dx_0 \\ &= \frac{1}{d} \int_A^{A+d} \left[x_0 + \frac{d}{2} - d \sum F(x_i) \right] dx_0 \\ &= (A + d) - \sum \int_A^{A+d} F(x_0 - id)\, dx_0 . \\ &= (A + d) - \int_{A-kd}^{A+d} F(x)\, dx. \end{aligned} \tag{18}$$

Integrating (18) by parts:

$$E(\hat{\mu}) = \int_{A-kd}^{A+d} x f(x)\, dx. \tag{19}$$

If the doses extend over a wide enough range, (19) indicates that $\hat{\mu}$ has a negligible bias:

$$E(\hat{\mu}) \doteq \mu. \tag{20}$$

For x_0 randomly chosen on $(A, A + d)$ the variance of $\hat{\mu}$ can be written:

$$\begin{aligned} V(\hat{\mu}) = E(\hat{\mu} - \mu)^2 &= E_{x_0}[V(\hat{\mu} \mid x_0) + B^2(\hat{\mu} \mid x_0)] \\ &= \frac{1}{d} \int_A^{A+d} \frac{d^2}{n} \sum F(x_i)[1 - F(x_i)]\, dx_0 + \frac{1}{d} \int_A^{A+d} B^2(\hat{\mu} \mid x_0)\, dx_0 . \\ V(\hat{\mu}) &= \frac{d}{n} \int_{A-kd}^{A+d} F(x)[1 - F(x)]\, dx + \frac{1}{d} \int_A^{A+d} B^2(\hat{\mu} \mid x_0)\, dx_0 . \end{aligned} \tag{21}$$

If the doses extend over a range such that the first integral in (21) is approximated to the degree desired by integrating over the infinite range, $V(\hat{\mu})$ can be written

$$V(\hat{\mu}) = \frac{d}{n}\int_{-\infty}^{\infty} F(x)[1 - F(x)]\,dx + \frac{1}{d}\int_{A}^{A+d} B^2(\hat{\mu} \mid x_0)\,dx_0 . \qquad (22)$$

The first integral has the value $(d \ln 2)/n$. It follows from (22) that

$$\frac{\left| V(\hat{\mu}) - \dfrac{d \ln 2}{n} \right|}{\dfrac{d \ln 2}{n}} \leqq \frac{n}{d \ln 2}\,[\max_{x_0} B^2(\hat{\mu} \mid x_0)]. \qquad (23)$$

From (23) and the numerical results in (12) the following bounds for the approximation of $V(\hat{\mu})$ by $(d \ln 2)/n$ can by obtained:

$$\begin{aligned} a = 4, \qquad d = \ln 4: \quad & \frac{\left| V(\hat{\mu}) - \dfrac{d \ln 2}{n} \right|}{\dfrac{d \ln 2}{n}} \leqq (3.76n)10^{-6}, \\ a = 10, \qquad d = \ln 10: \quad & \frac{\left| V(\hat{\mu}) - \dfrac{d \ln 2}{n} \right|}{\dfrac{d \ln 2}{n}} \leqq (1.09n)10^{-3}. \end{aligned} \qquad (24)$$

A summary of the results (20) and (24), for randomly chosen x_0, would be essentially the same as (17), i.e., if the doses extend over a wide enough range,

$$E(\hat{\mu}) \doteq \mu, \qquad V(\hat{\mu}) \doteq \frac{d \ln 2}{n}. \qquad (25)$$

In concluding the remarks on the properties of $\hat{\mu}$, it should be remarked that the distribution of $\hat{\mu}$, conditional on x_0, is asymptotically normal, since it is a linear function (3) of the sum of $k + 1$ binomially distributed random variables.

4. ESTIMATION OF θ

The point estimator of θ based on $\hat{\mu}$ was defined in (5). The expected value of this estimator can be approximated for random choice of x_0 as follows:

$$\begin{aligned} E(\hat{\theta}) = E[e^{-\gamma-\hat{\mu}}] &= E[e^{-(\gamma+\mu)-(\hat{\mu}-\mu)}] \\ &= \theta E[e^{-(\hat{\mu}-\mu)}] = \theta E\left[\sum_{i=0}^{\infty} \frac{(\hat{\mu} - \mu)^i}{i!}\right] \end{aligned} \qquad (26)$$

If the expectation is taken termwise in (26), terms in moments of order three and higher are dropped, and the approximation (25) is used, (26) can be written:

$$E(\hat{\theta}) \doteq \theta\left[1 + \frac{d \ln 2}{2n}\right]. \tag{27}$$

From (27) an estimator that is less biased than $\hat{\theta}$ is

$$\hat{\theta}' = \frac{2n}{2n + d \ln 2}\,\hat{\theta}. \tag{28}$$

The coefficient of variation of $\hat{\theta}$, C.V. $(\hat{\theta})$, can be approximated using (5) and (24):

$$C.V.(\hat{\theta}) = \frac{\sqrt{V(\hat{\theta})}}{\theta} \doteq \frac{\sqrt{\theta^2 V(\hat{\mu})}}{\theta} \doteq \sqrt{\frac{d \ln 2}{n}}. \tag{29}$$

The approximation to the variance of $\hat{\mu}$, given in (17) and in (25), is identical with the asymptotic variance of the estimator for $\ln \theta$ proposed by Fisher [5]. Therefore the asymptotic efficiency of the two procedures for estimating θ will be the same, 88 percent.

The interval estimator of θ given in (8) follows directly from (4), (17) and (25), and the asymptotic normality of $\hat{\mu}$.

5. DESIGN OF THE SERIAL DILUTION ASSAY

In choosing the range of dilutions, the conditions $F(x_0) \geq .99$ and $F(x_0 - kd) \leq .01$ should be satisfied. This implies that the expected number of organisms per dose at the highest and lowest concentrations should be greater than 5 and less than .01 respectively.

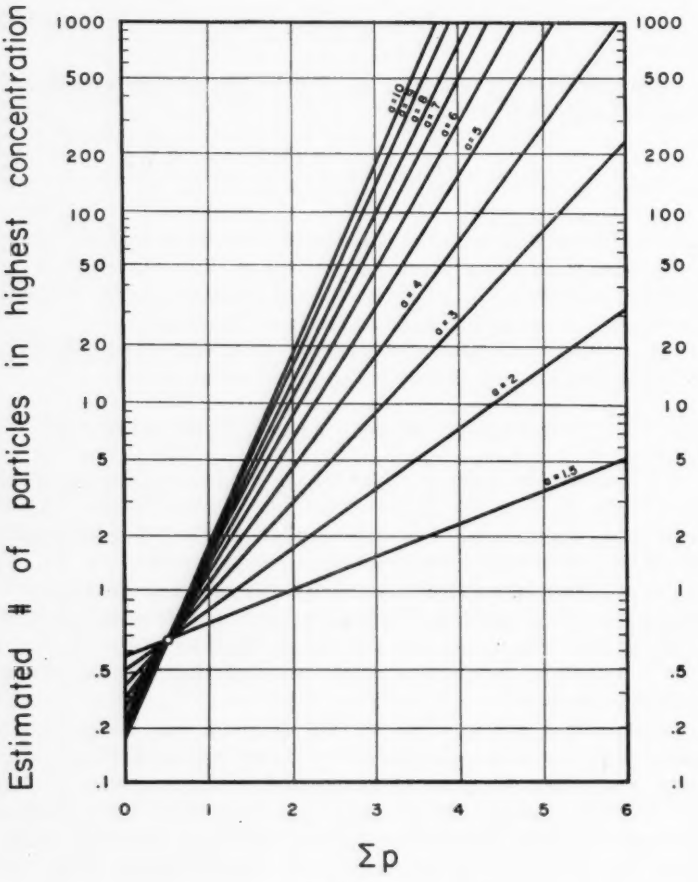
In designing a serial dilution assay the precision desired of the estimator must be specified. This can be done by specifying the desired value of the coefficient of variation (29). Then equation (29) can be used to obtain n, the number of tubes per dilution, for any dilution constant a desired.

Alternatively the precision of the estimator can be specified in terms of the interval estimator of θ. Using (8), the precision of the interval estimator for θ can be expressed in terms of the factor, $R = e^{1.96\sqrt{d \ln 2/n}} > 1$, which will be multiplied and divided into $\hat{\theta}$ to obtain the upper and lower limits of the 95 percent confidence interval. Graph 2 shows the values of R as functions of the dilution factor a for values of n from one to ten. This graph can be used to design dilution assays having desired precision. See the example in Section 6.

6. EXAMPLE OF DESIGN AND ANALYSIS

Suppose it is known that the density of organisms θ is between 10^2 and 10^5 organisms per unit volume. Suppose a ten-fold dilution factor is to be used. To assure doses spanning the range .01 to 5 organisms per dose, it is necessary to use concentrations ranging from 10^{-1} to 10^{-7} dilutions of the original suspension, or 7 dilutions altogether.

Suppose the value of θ is desired to within approximately four fold



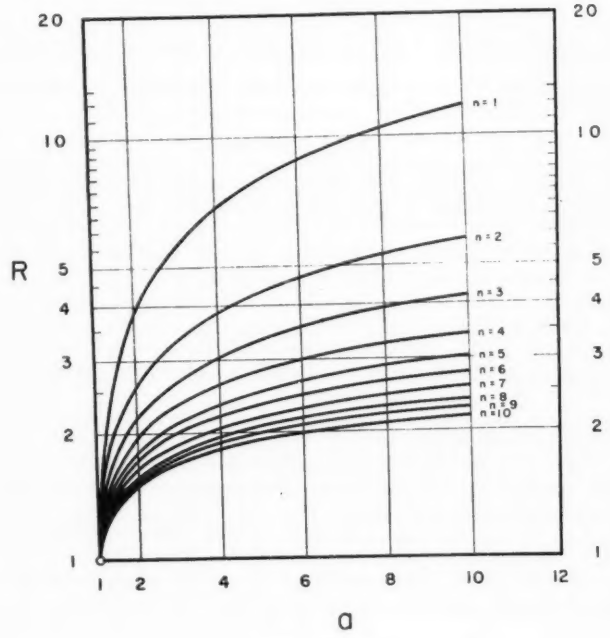
GRAPH 1

DENSITY ESTIMATES AS A FUNCTION OF $\sum p$ AND σ

TABLE I

ILLUSTRATIVE DATA

Dilution	Proportion of Tubes Showing Growth p
10^{-1}	3/3
10^{-2}	3/3
10^{-3}	2/3
10^{-4}	0/3
10^{-5}	0/3
10^{-6}	0/3
10^{-7}	0/3
	$\sum p = 8/3$



GRAPH 2

THE 95 PER CENT CONFIDENCE FACTOR (R) FOR COMBINATIONS OF n AND a

in either direction (i.e., the desired value of R is approximately 4). From Graph 2, $n = 3$ tubes per dilution will give $R = 4.2$ for a dilution factor of 10. This means a total sample size of $7n = 21$ tubes. In Table 1 some data and computational results are presented for such a design.

Using Graph 1, $z_0\hat{\theta} \doteq 80$ organisms per dose at the highest concentration, 10^{-1}. Therefore, $\hat{\theta} \doteq 800$ organisms per unit volume of the original suspension. Without Graph 1, $\hat{\theta}$ would be computed as follows:

$$\hat{\mu} = \ln 10^{-1} + \frac{\ln 10}{2} - (\ln 10)\left(\frac{8}{3}\right) = -7.2915,$$

$\hat{\theta} = e^{-\gamma - \hat{\mu}} = 824$ organisms per unit volume of the original suspension.

The interval estimate of $\hat{\theta}$ is obtained by using the factor R $(= 4.2)$ read from Graph 2:

$$\frac{824}{4.2} < \theta < 824(4.2),$$

$$196 < \theta < 3460 \text{ (confidence coefficient of .95).}$$

The point estimate $\hat{\theta}$ can be corrected for bias using equation (28):

$$\hat{\theta}' = \frac{2n}{2n + d \ln 2}\,\hat{\theta} = (.79)(824) = 651 \text{ organisms per unit volume.}$$

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THE FITTING OF A GENERALIZATION OF THE LOGISTIC CURVE

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This paper describes the fitting of the four-parameter family of curves defined by the differential equation.

$$\frac{dW}{dt} = \kappa W\left[1 - \left(\frac{W}{A}\right)^{1/\theta}\right] \tag{1}$$

Special cases were originally proposed by Pütter [1920] for various types of animal growth (see e.g. von Bertalanffy [1957]), and recently Richards [1959] has exemplified the general form of the curves and suggested that they may be useful for the empirical description of plant growth. For further details of the history of these curves and their mathematical properties reference should be made to Richards' paper. It suffices to say here that the family defined by (1) includes as special cases several curves which have been used empirically for the description of growth, including the 'monomolecular' (diminishing returns) curve ($\theta = -1$), the exponential curve ($\theta \to 0$ through positive values), the logistic curve ($\theta = 1$), and the Gompertz curve ($\theta \to \infty$ with A fixed and κ a linear function of θ).

MODEL AND NOTATION

In using (1) in the description of growth, W will usually denote a weight of some kind, while t is usually chronological time, but may be a suitable 'time scale' (Skellam *et al.* [1959], Nelder *et al.* [1960]) which can replace chronological time when the environment is variable. Since it seems to be characteristic of many growth phenomena that the relative growth rate ($W^{-1}\, dW/dt$) is almost constant when the weight is small compared to the final weight, we shall restrict θ to be positive in what follows. For if $\theta < 0$, then, for W sufficiently small, $W^{-1}\, dW/dt$ becomes as large as we please in absolute value. When $\theta > 0$, the solution of (1) can be written in the form

$$W = A/\{1 + e^{-(\lambda + \kappa t)/\theta}\}^{\theta} \tag{2}$$

where λ is the constant of integration. A and κ are taken as positive since W is positive and is assumed to increase with time. Thus $W^{1/\theta}$ satisfies the logistic equation with upper asymptote $A^{1/\theta}$ as $t \geq \infty$, while for t large and negative

$$W \sim Ae^{\lambda+\kappa t}.$$

We now write $Y = \ln W$ and $\alpha = \ln A$ so that

$$Y = \alpha - \theta \ln [1 + e^{(\lambda+\kappa t)/\theta}] \tag{3}$$

where ln denotes the natural logarithm. (3) is the form of the equation that will be used for fitting, and we shall assume that if $y = \ln w$ is a sample value of $Y = \ln W$ at time t, then $E(y) = Y$, and var $y = \sigma^2$ independently of Y. We shall also assume that the y_i $(i = 1, \cdots, n)$ obtained at time t_i, i.e. the sample points to which the curve is to be fitted, are independent. The independence condition is satisfied for instance in plant growth analysis when a randomized field layout is used, and the sampling is destructive, i.e., a different set of plants is taken on each occasion. When the same set of plants is used on each occasion (when w might denote leaf area measured non-destructively) it is still possible to use the method proposed for estimation, though of course sampling variances cannot be obtained from residual mean squares 'within curves' if the condition of independence is not satisfied. This situation is further discussed later in the paper.

The assumption that $y = \ln w$ has constant variance has been found to be reasonable from an examination of data on the weight of part or the whole of several crops. In fact it is usually found that the distribution of y does not differ significantly from a normal distribution.

For the purposes of this paper, (2) will be described as the *generalized logistic equation*, though it is not of course the only generalization that could or has been made from the logistic equation.

FITTING THE LOGISTIC CURVE

We consider first the case where θ is known. This is equivalent to fitting the logistic equation, since by putting $W' = W^{1/\theta}$, $Y' = Y/\theta$, $\alpha' = \alpha/\theta$, $\lambda' = \lambda/\theta$ and $\kappa' = \kappa/\theta$ we can convert (2) into the logistic function. We may, therefore, put $\theta = 1$ for this case without loss of generality. Let us write

$$\tau_i = \lambda + \kappa t_i \quad \text{and} \quad \xi_i = \frac{e^{-\tau_i}}{1 + e^{-\tau_i}} = \frac{1}{1 + e^{\tau_i}} = \frac{A - W_i}{A};$$

then from (3)

$$Y_i = \alpha + \ln(1 - \xi_i), \quad \frac{\partial Y_i}{\partial \alpha} = 1, \quad \frac{\partial Y_i}{\partial \lambda} = \xi_i, \quad \text{and} \quad \frac{\partial Y_i}{\partial \kappa} = \xi_i t_i,$$

Thus the least-square equations are given by

$$\begin{aligned} \sum_i (y_i - Y_i) &= 0, \\ \sum_i (y_i - Y_i)\xi_i &= 0, \\ \sum_i (y_i - Y_i)\xi_i t_i &= 0. \end{aligned} \tag{4}$$

These equations have no explicit solution in general, so that they must be solved by iteration. The usual method, using the expected values of the information matrix (see e.g. Bailey [1951]), gives the following

TABLE I

EXTENSION OF BERKSON'S TABLE OF ANTI-LOGITS $[1/1 + e^{-\tau})]$

τ	0	1	2	3	4	5	6	7	8	9
					0.99					
5.0	331	337	344	350	357	363	369	376	382	388
5.1	394	400	406	412	418	423	429	435	440	446
5.2	451	457	462	467	473	478	483	488	493	498
5.3	503	508	513	518	523	527	532	537	541	546
5.4	550	555	559	564	568	572	576	581	585	589
5.5	593	597	601	605	609	613	617	620	624	628
5.6	632	635	639	642	646	649	653	656	660	663
5.7	667	670	673	676	680	683	686	689	692	695
5.8	698	701	704	707	710	713	716	719	721	724
5.9	727	730	732	735	737	740	743	745	748	750
6.0	753	755	758	760	762	765	767	769	772	774
6.1	776	778	781	783	785	787	789	791	793	795
6.2	797	799	801	803	805	807	809	811	813	815
6.3	817	819	820	822	824	826	827	829	831	832
6.4	834	836	837	839	841	842	844	845	847	848
6.5	850	851	853	854	856	857	859	860	861	863
6.6	864	865	867	868	869	871	872	873	875	876
6.7	877	878	879	881	882	883	884	885	887	888
6.8	889	890	891	892	893	894	895	896	897	898
6.9	899	900	901	902	903	904	905	906	907	908

To obtain ξ, from this table and Berkson's table in Berkson [1953], use the formula, ξ = antilogit $(-\tau)$ = 1 − antilogit (τ).

TABLE II

VALUES OF $10^4 \ln (1 + e^{-\tau})$

For τ positive $-\ln (1 - \xi)$ = tabulated value.
For τ negative $-\ln (1 - \xi) = |\tau|$ + tabulated value for $|\tau|$.

τ	0	1	2	3	4	5	6	7	8	9
0.0	6931	6882	6832	6783	6733	6685	6636	6588	6539	6492
0.1	6444	6397	6349	6303	6256	6210	6163	6118	6072	6027
0.2	5981	5936	5892	5847	5803	5759	5716	5672	5629	5586
0.3	5544	5501	5459	5417	5375	5334	5293	5252	5211	5170
0.4	5130	5090	5050	5011	4972	4932	4894	4855	4817	4779
0.5	4741	4703	4666	4629	4592	4555	4518	4482	4446	4410
0.6	4375	4340	4304	4270	4235	4201	4166	4132	4099	4065
0.7	4032	3999	3966	3933	3901	3869	3837	3805	3773	3742
0.8	3711	3680	3649	3619	3589	3559	3529	3499	3470	3441
0.9	3412	3383	3354	3326	3298	3270	3242	3214	3187	3160
1.0	3133	3106	3079	3053	3027	3001	2975	2949	2924	2898
1.1	2873	2848	2824	2799	2775	2751	2727	2703	2679	2656
1.2	2633	2610	2587	2564	2542	2519	2497	2475	2453	2432
1.3	2410	2389	2368	2347	2326	2305	2285	2264	2244	2224
1.4	2204	2184	2165	2146	2126	2107	2088	2070	2051	2032
1.5	2014	1996	1978	1960	1942	1925	1907	1890	1873	1856
1.6	1839	1822	1806	1789	1773	1757	1741	1725	1709	1693
1.7	1678	1662	1647	1632	1617	1602	1588	1573	1558	1544
1.8	1530	1516	1502	1488	1474	1460	1447	1433	1420	1407
1.9	1394	1381	1368	1355	1343	1330	1318	1306	1293	1281
2.0	1269	1257	1246	1234	1222	1211	1200	1188	1177	1166
2.1	1155	1144	1134	1123	1112	1102	1091	1081	1071	1061
2.2	1051	1041	1031	1021	1012	1002	993	983	974	965
2.3	955	946	937	928	920	911	902	894	885	877
2.4	868	860	852	844	836	828	820	812	804	796
2.5	789	781	774	766	759	752	745	737	730	723
2.6	716	710	703	696	689	683	676	670	663	657
2.7	650	644	638	632	626	620	614	608	602	596
2.8	590	585	579	573	568	562	557	551	546	541
2.9	536	530	525	520	515	510	505	500	495	491
3.0	486	481	476	472	467	463	458	454	449	445
3.1	441	436	432	428	424	420	415	411	407	403
3.2	399	396	392	388	384	380	377	373	369	366
3.3	362	359	355	352	348	345	341	338	335	331
3.4	328	325	322	319	316	312	309	306	303	300
3.5	297	295	292	289	286	283	280	278	275	272
3.6	270	267	264	262	259	257	254	252	249	247
3.7	244	242	239	237	235	232	230	228	226	223
3.8	221	219	217	215	213	211	208	206	204	202
3.9	200	198	196	195	193	191	189	187	185	183
4.0	181	180	178	176	174	173	171	169	168	166
4.1	164	163	161	160	158	156	155	153	152	150
4.2	149	147	146	144	143	142	140	139	137	136
4.3	135	133	132	131	130	128	127	126	124	123
4.4	122	121	120	118	117	116	115	114	113	112
4.5	110	109	108	107	106	105	104	103	102	101

TABLE II—(*Continued*)

τ		τ		τ		τ		τ	
4.60	100	5.10	61	5.60	37	6.10	22	6.60	14
4.70	91	5.20	55	5.70	33	6.20	20	6.70	12
4.80	82	5.30	50	5.80	30	6.30	18	6.80	11
4.90	74	5.40	45	5.90	27	6.40	17	6.90	10
5.00	67	5.50	41	6.00	25	6.50	15	—	—

adjustments $\delta\alpha_0$, $\delta\lambda_0$, $\delta\kappa_0$ to initial 'guesses' α_0 , λ_0 , κ_0 for the parameters:—

$$\begin{bmatrix} n & \sum \xi_i & \sum \xi_i t_i \\ & \sum \xi_i^2 & \sum \xi_i^2 t_i \\ & & \sum \xi_i^2 t_i^2 \end{bmatrix} \begin{bmatrix} \delta\alpha_0 \\ \delta\lambda_0 \\ \delta\kappa_0 \end{bmatrix} = \begin{bmatrix} \sum (y_i - Y_i) \\ \sum \xi_i (y_i - Y_i) \\ \sum \xi_i t_i (y_i - Y_i) \end{bmatrix} \tag{5}$$

where ξ_i is evaluated with $\lambda = \lambda_0$ and $\kappa = \kappa_0$. New values of ξ_i and Y_i are then recalculated using $\alpha_1 = \alpha_0 + \delta\alpha_0$ etc. and further adjustments obtained, the process being repeated until whatever accuracy required is achieved. Note that the information matrix depends on the parameters only through τ_i ; the process of solution of (5) would obviously be considerably speeded up if tables of ξ_i and ln $(1 - \xi_i)$ as functions of τ_i were available.

Now ξ = antilogit $(-\tau)$ = 1 − antilogit (τ) in Berkson's [1953] notation; hence ξ can be obtained for the range $-4.99 \leq \tau \leq 4.99$ from the table of antilogits given in that paper. An extension of this table for $5 \leq |\tau| \leq 6.99$ which covers the region down to $W/A = 0.001$ and up to $W/A = 0.999$ is given in Table I. Values of ln $(1 + e^{-\tau})$ to four decimal places are given in Table II for $-6.99(0.01)6.99$ from which ln $(1 - \xi)$ can be quickly derived. These tables have been computed from the tables of e^x and ln x given in Comrie [1949] and should prove sufficiently accurate for most purposes. If linear interpolation is used from the nearest tabulated value, using the tabulated first difference, rounding-off errors will rarely exceed 1 unit in the last place.

Because Y_i is linear in α, knowledge of its approximate value is not necessary for the iterative process using the expected information matrix, and we can replace $\delta\alpha_0$ in (5) by α_1 , and Y by ln $(1 - \xi)$, solving directly for α_1 , $\delta\lambda_0$ and $\delta\kappa_0$. However when we come to consider the exact equations for the iteration, using the empirical information matrix

instead of the expected one, we shall find no advantage in suppressing α_0 , so that it will be retained in what follows. The calculations can be conveniently laid out as follows:

TABLE III

COMPUTING LAYOUT FOR FITTING THE LOGISTIC CURVE

(1)	(2)	(3)	(4)	(5)	(6)	(7)
t_i	$\tau_i = \lambda + \kappa t_i$	ξ_i	$\xi_i t_i$	$\ln (1 - \xi_i)$	y_i	$y_i - Y_i$

The t_i are entered in column 1, whence the τ_i are calculated using the starting values of λ and κ, and entered in column 2. Column 3 is filled up from Table I, and then column 4 calculated. Column 5 is filled up from Table II, and the y's entered in column 6. α is estimated by $\bar{y} - \sum \ln (1 - \xi_i)/n$ from the sums of columns 5 and 6, and hence $y_i - Y_i = y_i - \alpha - \ln (1 - \xi_i)$ is calculated. The coefficients on the left-hand side of (5) can now be calculated from columns 3 and 4, by summing the columns and from sums of squares and products of ξ_i and $\xi_i t_i$. Finally the right-hand side of (4) may be calculated from $\sum (y_i - Y_i)$, which should be zero, apart from rounding errors, and from products of columns 3 and 4 with column 7. The equations (4) may now be solved using any of the standard techniques (see e.g., Dwyer [1951]).

The exact iterative equations

If we now denote the parameters to be fitted by θ_i , then the above method uses the expected information matrix whose general term is

$$\sum_x \frac{\partial Y_x}{\partial \theta_i} \frac{\partial Y_x}{\partial \theta_j}.$$

The exact equations for the generalized Newton-Raphson process are those using the empirical information matrix with general term

$$\sum_x \frac{\partial Y_x}{\partial \theta_i} \frac{\partial Y_x}{\partial \theta_j} - \sum_x (y_x - Y_x) \frac{\partial^2 Y_x}{\partial \theta_i \partial \theta_j}.$$

Cornfield and Mantel [1950] for the analogous situation in probit analysis found a substantial improvement in the speed of convergence using this latter form, so that it may be worth considering the appropriate modification here. This necessitates adding to the left-hand-side of (5) the matrix

$$\begin{bmatrix} 0 & 0 & 0 \\ & \sum (y_i - Y_i)\xi_i(1-\xi_i) & \sum (y_i - Y_i)\xi_i(1-\xi_i)t_i \\ & & \sum (y_i - Y_i)\xi_i(1-\xi_i)t_i^2 \end{bmatrix}$$

and two more columns need to be added to Table III, namely $(y - Y)(1 - \xi)$ and ξt^2 in order to compute the elements of this matrix. The extra calculation is not large but the increase in speed of convergence achieved may justify the extra labour only when σ^2 is large so that the $(y_i - Y_i)$ are appreciable.

The dispersion matrix of the estimates of the parameters may be obtained in the usual way by inverting the information matrix on the left-hand side of (5) and then multiplying it by an estimate of σ^2. For methods of matrix inversion, and the combination of the inversion with the solution of an associated set of equations, see e.g., Dwyer [1951].

If a variance for $\hat{A}$ rather than $\hat{\alpha}$ is wanted, then we may use the approximate formula

$$\text{var } \hat{A} = \text{var } e^{\hat{\alpha}} \sim e^{2\hat{\alpha}} \text{ var } \hat{\alpha} = \hat{A}^2 \text{ var } \hat{\alpha}$$

provided that var $\hat{A}$ is small compared to $\hat{A}^2$.

Obtaining the starting values

The starting values may be obtained in various ways, some wholly graphical and some partly so. Some compromise must be made between the desirability of having them as accurate as possible so that iterations are reduced to a minimum, and the undesirability of spending an excessive amount of time on a preliminary stage of the computations.

A semi-graphical method which I have found useful is as follows. First plot the logistic variable $w^{1/\theta}$, henceforth denoted by x, against t, and estimate by eye the value of A; call this estimate A'. Then plot $\ln [x/(A' - x)]$ against t. If the logistic function is the correct one and A' is also correct, this should give, apart from random errors, a straight line. Now the variance of $\ln [x/(A - x)]$ using the first-order approximation, is given by $[A/(A - x)]^2\sigma^2 = \xi^2\sigma^2$ in the notation already established. This variance increases as x increases, tending to infinity as x tends to A. Thus when the variance of x is constant, the graph of $\ln [x/(A' - x)]$ against t will show increasing scatter as x approaches A. In addition, if x has a symmetrical distribution, that of $\ln [x/(A - x)]$ will be positively skewed for x near A and positive deviations will be in mean value much greater than negative ones. If A' is too high, then the graph of $\ln [x/(A' - x)]$ against t will show a tendency to level off at $\ln [A/(A' - A)]$, while if A' is too low, the

graph will show an increasing slope as x approaches A. If the graph shows a sigmoid shape, the logistic equation is inappropriate. Assuming that no sigmoid shape has been found, we may obtain an improved estimate of A as follows. Divide the points into two sets, with the dividing line roughly where $x = A'/2$; then points with $x < A'/2$ are relatively slightly affected by errors in A, and have the smallest variances. Fit by eye a straight line to the points on the $(\ln [x/(A' - x)], t)$-graph using the points where $x < A'/2$ and giving most weight to the smaller values of x. Read off the fitted values of $x/(A - x)$ on this line corresponding to the values of t for points having $x > A'/2$. If z is such a fitted value, then, ignoring errors, $z = x/(A - x)$ and so $A = x(1 + z)/z$. Hence if we write $u = x(1 + z)/z$, then u is an estimate of A. To obtain an improved value for A, calculate u for each point having $x > A'/2$ and use $\bar{u}$, the simple mean of the u's. The method is quite rapid in practice if a logarithmic graph paper is used, since then $\ln [x/(A' - x)]$ can be plotted directly from a knowledge of $x/(A' - x)$ and z can also be read off directly from the fitted line. If the improved value of A still gives curvature, the process may be repeated. Having obtained a good value for A_0 , the starting value for A, we may now calculate λ_0 and κ_0 either by a graphical fitting of a straight line to the graph of $\ln [x/(A_0 - x)]$ against t, using the relation $\ln [X/(A_0 - X)] = \lambda + \kappa t$ or by a weighted regression of $\ln [x/(A_0 - x)]$ on t using as weights $\xi_0^2 = [(A_0 - x)/A_0]^2$. When

TABLE IV

CALCULATIONS TO OBTAIN STARTING VALUES FOR FITTING THE LOGISTIC CURVE

t	x	$x/(71 - x)$	$u = x(1 + z)/z$	$x/(73.2 - x)$
−2.15	3.57	0.0529		0.0513
−1.50	6.25	0.0965		0.0934
−0.85	9.54	0.155		0.150
−0.08	16.91	0.313		0.300
+0.52	24.51	0.510		0.503
1.10	33.78	0.908		0.857
2.28	50.00	2.38	71.9	2.16
3.23	62.05	6.93	74.0	5.57
4.00	69.34	41.8	76.5	18.0
4.65	67.09	17.2	71.1	11.0
5.00	69.34	41.8	72.4	18.0
			Mean 73.2	

σ^2 is small, the fit by eye should be quite adequate, but the weighted regression may have some advantage when the scatter about the line is considerable. If logarithmic paper is used, it must be remembered that one cycle corresponds to $\log_e 10 = 2.30259$ units when the slope is to be measured.

Worked example

The data in Table IV relate to the growth of carrot tops in a field experiment, and were obtained by my colleague Mr. R. B. Austin. θ has been taken as known and equal to 2, so that x, the logistic variable, equals $W^{1/2}$; t is a time scale based on total incoming radiation (negative values occur because an origin had been taken with a zero between

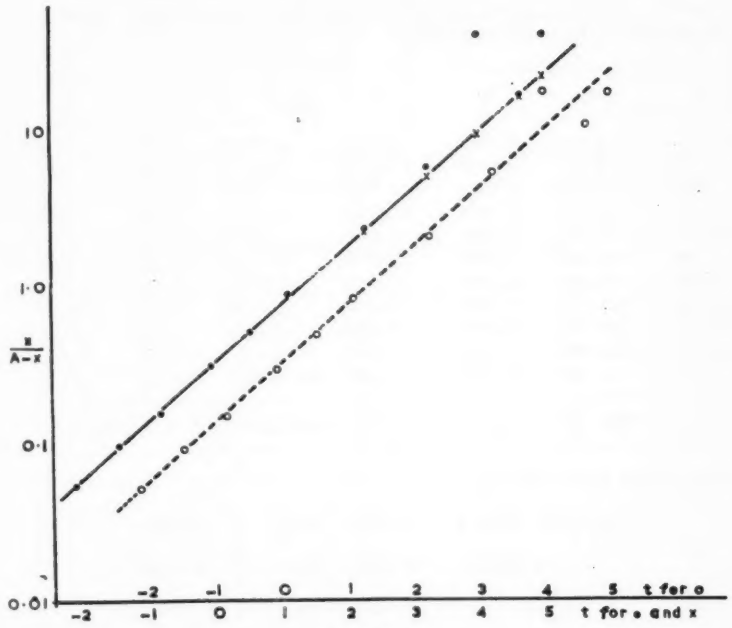

FIGURE 1

METHOD OF OBTAINING STARTING VALUES FOR α, λ, κ, FROM DATA OF TABLE IV.

● Values of $x/(71 - x)$ plotted on logarithmic scale against t.
× Fitted values of $Z = (x/A - x)$ obtained from line drawn by eye through points having $x < 35.5$.
○ Values of $x/(73.2 - x)$ plotted on logarithmic scale against t.
[Note: t – scale displaced to avoid overlapping]
- - - Line fitted by eye through points ○.

the fourth and fifth reading; the reasons for this have no relevance for this example). Table IV also contains the preliminary calculations necessary to arrive at A_0, the starting value for A. An initial plot of x against t gave an A', as judged by eye, of 71. $x/(71 - x)$ was then calculated and recorded in the third column of Table IV. Figure 1 shows the graph of $\ln [x/(71 - x)]$ against t. From the solid line fitted by eye to the points having $x < A'/2 = 35.5$, the fitted values of $x/(A - x)$ for the last 5 points were read off, with u calculated for each, and recorded in the fourth column of Table IV. The revised value of A' is $\bar{u} = 73.2$. Values of $x/(73.2 - x)$ were then calculated (fifth column of Table IV) and plotted against t (Figure 1); the broken line was fitted by eye, giving most weight to the small values of x, and gave $\lambda_0 = -1.109$, $\kappa_0 = 0.861$. The calculations for the exact iterative method discussed above can now be started. Filling up Table III we have the following:

t_i	τ_i	ξ_i	$\xi_i t_i$	$\ln(1 - \xi_i)$	y_i	$y_i - Y_i$
−2.15	−2.960	0.9507	−2.0440	−3.0105	1.272	−0.0020
−1.50	−2.400	0.9168	−1.3752	−2.4868	1.832	+0.0343
−0.85	−1.841	0.8631	−0.7336	−1.9883	2.255	−0.0412
−0.08	−1.178	0.7646	−0.0612	−1.4464	2.828	−0.0101
+0.52	−0.661	0.6595	+0.3429	−1.0773	3.199	−0.0082
+1.10	−0.162	0.5404	0.5944	−0.7774	3.520	+0.0129
+2.28	+0.854	0.2986	0.6808	−0.3547	3.912	−0.0178
+3.23	+1.672	0.1582	0.5110	−0.1722	4.128	+0.0157
+4.00	+2.335	0.0883	0.3532	−0.0924	4.239	+0.0469
+4.65	+2.895	0.0524	0.2437	−0.0538	4.206	−0.0247
+5.00	+3.196	0.0393	0.1965	−0.0401	4.239	−0.0054

$\bar{y} = 3.2391, \sum(1 - \xi_i)/n = -1.0454, \alpha_0 = 4.2845, S.S. = 0.00661578.$

Adjustment equations are

$$\begin{bmatrix} 11.0000 & 5.3319 & -1.2915 \\ & 3.9272 & -3.0008 \\ & & 8.0293 \end{bmatrix} \begin{bmatrix} \delta\alpha_0 \\ \delta\lambda_0 \\ \delta\kappa_0 \end{bmatrix} = \begin{bmatrix} 0.0004 \\ -0.0124 \\ -0.0020 \end{bmatrix}.$$

Solution is given by

$$\begin{aligned} \delta\alpha_0 &= 0.010025, & & & \alpha_1 &= 4.2940, \\ \delta\lambda_0 &= -0.021566, & \text{from} & \text{whence} & \lambda_1 &= -1.1300, \\ \delta\kappa_0 &= -0.006746, & & & \kappa_1 &= 0.8544. \end{aligned}$$

If a further iteration is required then α_1 should be estimated in the same way as α_0 , i.e. using $\bar{y} - \sum \ln (1 - \xi_i)/n$, and the value obtained above ignored. However the adjustments obtained from the first cycle are sufficiently small to justify our stopping in this case.

The goodness of fit of the logistic curve can now be checked by comparing the residual mean square after fitting with the residual error obtained from replication. Using the estimates α_1 , λ_1 , κ_1 , we have a residual sum of squares after fitting of 0.00642 giving a mean square with $11 - 3 = 8$ d.f. of 0.00080. The error mean square was 0.0033 so that the fit is satisfactory. We may now obtain the dispersion matrix by inverting the information matrix and multiplying it by the variance of a single y_i , as estimated by the error mean square. Thus the dispersion matrix is given by

$$0.0033 \times \begin{bmatrix} 11.0000 & 5.3319 & -1.2915 \\ & 3.9272 & -3.0008 \\ & & 8.0293 \end{bmatrix}^{-1} = \begin{bmatrix} 0.00137 & -0.00237 & 0.00066 \\ & 0.00526 & 0.00159 \\ & & 0.00090 \end{bmatrix}$$

The standard errors of the estimates affect the second place of decimals, thus justifying the stopping of the iterative process after one cycle.

FITTING THE GENERALIZED LOGISTIC CURVE

If we now define τ_i as $(\lambda + \kappa t_i)/\theta$, then from (2)

$$Y = \alpha + \theta \ln (1 - \xi)$$

where $\xi = e^{-\tau}/(1 + e^{-\tau})$ as before, and

$$\frac{\partial Y_i}{\partial \alpha} = 1, \quad \frac{\partial Y_i}{\partial \lambda} = \xi_i , \quad \frac{\partial Y_i}{\partial \kappa} = \xi_i t_i , \quad \frac{\partial Y_i}{\partial \theta} = \ln (1 - \xi_i) - \tau_i \xi_i = \beta_i , \text{ say.}$$

The least-square equations, therefore, are given by

$$\begin{aligned} \sum (y_i - Y_i) &= 0, & \sum (y_i - Y_i)\xi_i t_i &= 0, \\ \sum (y_i - Y_i)\xi_i &= 0, & \sum (y_i - Y_i)\beta_i &= 0 \end{aligned} \tag{6}$$

and the iterative solution from starting values α_0 , λ_0 , κ_0 , θ_0 , gives adjustments $\delta\alpha_0$ etc. from the solution of

$$\begin{bmatrix} n & \sum \xi_i & \sum \xi_i t_i & \sum \beta_i \\ & \sum \xi_i^2 & \sum \xi_i^2 t_i & \sum \beta_i \xi_i \\ & & \sum \xi_i^2 t_i^2 & \sum \beta_i \xi_i t_i \\ & & & \sum \beta_i^2 \end{bmatrix} \begin{bmatrix} \delta\alpha_0 \\ \delta\lambda_0 \\ \delta\kappa_0 \\ \delta\theta_0 \end{bmatrix} = \begin{bmatrix} \sum (y_i - Y_i) \\ \sum (y_i - Y_i)\xi_i \\ \sum (y_i - Y_i)\xi_i t_i \\ \sum (y_i - Y_i)\beta_i \end{bmatrix}. \tag{7}$$

TABLE V

VALUES OF $-10^4\beta$, $-\beta = \tau/(1 + e^{-\tau}) - \ln(1 + e^{\tau})$

τ	0	1	2	3	4	5	6	7	8	9
0.0	6931	6931	6931	6930	6929	6928	6927	6925	6923	6921
0.1	6919	6916	6913	6910	6907	6903	6900	6895	6891	6887
0.2	6882	6877	6871	6866	6860	6854	6848	6841	6834	6827
0.3	6820	6813	6805	6797	6789	6781	6772	6763	6754	6745
0.4	6735	6726	6716	6706	6695	6685	6674	6663	6652	6640
0.5	6628	6617	6605	6592	6580	6567	6554	6541	6528	6515
0.6	6501	6487	6473	6459	6445	6430	6415	6400	6385	6370
0.7	6355	6339	6323	6307	6291	6275	6258	6242	6225	6208
0.8	6191	6174	6157	6139	6122	6104	6086	6068	6050	6031
0.9	6013	5994	5976	5957	5938	5919	5900	5881	5861	5842
1.0	5822	5802	5782	5763	5743	5722	5702	5682	5662	5641
1.1	5620	5600	5579	5558	5537	5516	5495	5474	5453	5432
1.2	5411	5389	5368	5346	5325	5303	5281	5260	5238	5216
1.3	5194	5172	5150	5128	5106	5084	5062	5040	5018	4996
1.4	4974	4951	4929	4907	4885	4862	4840	4818	4795	4773
1.5	4751	4728	4706	4683	4661	4639	4616	4594	4571	4549
1.6	4527	4504	4482	4460	4437	4415	4393	4370	4348	4326
1.7	4304	4282	4259	4237	4215	4193	4171	4149	4127	4105
1.8	4083	4061	4039	4018	3996	3974	3952	3931	3909	3887
1.9	3866	3844	3823	3802	3780	3759	3738	3717	3695	3674
2.0	3653	3632	3611	3591	3570	3549	3528	3508	3487	3467
2.1	3446	3426	3406	3385	3365	3345	3325	3305	3285	3265
2.2	3245	3226	3206	3186	3167	3147	3128	3109	3090	3070
2.3	3051	3032	3013	2994	2976	2957	2938	2920	2901	2883
2.4	2864	2846	2828	2810	2792	2774	2756	2738	2721	2703
2.5	2685	2668	2650	2633	2616	2599	2582	2565	2548	2531
2.6	2514	2497	2481	2464	2448	2431	2415	2399	2383	2367
2.7	2351	2335	2319	2303	2288	2272	2257	2241	2226	2211
2.8	2195	2180	2165	2150	2136	2121	2106	2091	2077	2062
2.9	2048	2034	2020	2005	1991	1977	1964	1950	1936	1922
3.0	1909	1895	1882	1868	1855	1842	1829	1816	1803	1790
3.1	1777	1764	1752	1739	1726	1714	1702	1689	1677	1665
3.2	1653	1641	1629	1617	1605	1594	1582	1570	1559	1547
3.3	1536	1525	1514	1502	1491	1480	1469	1459	1448	1437
3.4	1426	1416	1405	1395	1384	1374	1364	1354	1344	1333
3.5	1323	1314	1304	1294	1284	1274	1265	1255	1246	1236
3.6	1227	1218	1208	1199	1190	1181	1172	1163	1154	1146
3.7	1137	1128	1120	1111	1102	1094	1086	1077	1069	1061
3.8	1053	1045	1037	1029	1021	1013	1005	997	989	982
3.9	974	967	959	952	944	937	930	922	915	908
4.0	901	894	887	880	873	866	859	853	846	839
4.1	833	826	820	813	807	800	794	788	782	775
4.2	769	763	757	751	745	739	733	728	722	716

TABLE V—(*Continued*)

r	0	1	2	3	4	5	6	7	8	9
4.3	710	705	699	694	688	682	677	672	666	661
4.4	656	650	645	640	635	630	625	620	615	610
4.5	605	600	595	590	586	581	576	572	567	562
4.6	558	553	549	544	540	536	531	527	523	518
4.7	514	510	506	502	498	494	490	486	482	478
4.8	474	470	466	462	458	455	451	447	444	440
4.9	436	433	429	426	422	419	415	412	408	405
5.0	402	398	395	392	389	386	382	379	376	373
5.1	370	367	364	361	358	355	352	349	346	343
5.2	340	337	335	332	329	326	324	321	318	316
5.3	313	310	308	305	303	300	298	295	293	290
5.4	288	285	283	281	278	276	274	271	269	267
5.5	265	262	260	258	256	254	252	249	247	245
5.6	243	241	239	237	235	233	231	229	227	225
5.7	223	222	220	218	216	214	212	211	209	207
5.8	205	204	202	200	198	197	195	193	192	190
5.9	188	187	185	184	182	181	179	178	176	175
6.0	173	172	170	169	167	166	164	163	162	160
6.1	159	158	156	155	154	152	151	150	148	147
6.2	146	145	143	142	141	140	138	137	136	135
6.3	134	133	132	130	129	128	127	126	125	124
6.4	123	122	121	120	119	118	116	116	114	114
6.5	113	112	111	110	109	108	107	106	105	104
6.6	103	102	101	101	100	99	98	97	96	95
6.7	95	94	93	92	91	91	90	89	88	88
6.8	87	86	85	85	84	83	82	82	81	80
6.9	80	79	78	77	77	76	75	75	74	73
7.0	73	72	72	71	70	70	69	69	68	67

Little amendment is needed to Table III for the solution of these equations. A column for β must be inserted between columns 4 and 5, and β can be obtained rapidly from Table V. α_0 is estimated as $\bar{y} - \theta_0 \cdot \sum \ln (1 - \xi_i)/n$, and $y_i - Y_i = y_i - \alpha_0 - \theta_0 \ln (1 - \xi_i)$. All the elements in (7) can then be calculated.

Obtaining the starting values

A sign that θ is not equal to unity is the appearance of a trend in the values of u during the graphical process for finding A_0. If $\theta > 1$, then values of u show a decreasing trend as w departs from A, and the lowest of them are often below the highest values of w. Conversely if $\theta < 1$, then u shows an increasing trend as w falls. According

to the trend shown by the u's, θ can be changed in the appropriate direction, and when θ_0 has been obtained, with the corresponding $A^{1/\theta}$, we can use the relation

$$E\left[\ln \frac{x^{1/\theta}}{A^{1/\theta} - x^{1/\theta}}\right] \sim \frac{1}{\theta}(\lambda + \kappa t) = \tau$$

to get estimate of λ_0/θ_0 and κ_0/θ_0 and hence of λ_0 and κ_0 . For the calculations of coefficients in (7), however, only t and τ are needed.

Worked example

In the example above of fitting the logistic curve to $W^{1/2}$, we were in fact fitting the generalized logistic curve taking θ as known and equal to 2. We now consider the fitting when θ is not assumed known, using the value 2 as a starting point. Columns 1–5 of Table III are unchanged but y in column 6 is now twice the previous value since we were working before with $\ln x^{1/2} = \frac{1}{2}\ln x$. Column 7 will also be doubled and a column of β_i must be added. The revised and added columns are given together with the iterative equations in Table VI.

TABLE VI

REVISED AND ADDITIONAL COLUMNS FOR FITTING THE GENERALIZED LOGISTIC CURVE

β_i	y_i	$y_i - Y_i$
−0.1964	2.544	−0.0038
−0.2865	3.664	+0.0688
−0.3992	4.510	−0.0824
−0.5457	5.656	−0.0200
−0.6414	6.398	−0.0162
−0.6895	7.040	+0.0252
−0.6096	7.824	+0.0356
−0.4366	8.256	+0.0314
−0.2987	8.478	+0.0942
−0.2054	8.412	−0.0494
−0.1657	8.478	−0.0106

Adjustment equations are

$$\begin{bmatrix} 11.0000 & 5.3319 & -1.2915 & -4.4747 \\ & 3.9273 & -3.0008 & -2.3015 \\ & & 8.0293 & -0.3343 \\ & & & 2.1857 \end{bmatrix} \begin{bmatrix} \delta\alpha_0 \\ \delta\lambda_0 \\ \delta\kappa_0 \\ \delta\theta_0 \end{bmatrix} = \begin{bmatrix} 0.0016 \\ -0.0244 \\ -0.0048 \\ 0.0096 \end{bmatrix}.$$

The solution of these equations is given by

$$\delta\alpha_0 = -0.016240,$$
$$\delta\lambda_0 = -0.201431,$$
$$\delta\kappa_0 = -0.089091,$$
$$\delta\theta_0 = -0.254585,$$

whence

$$\lambda_1 = \theta_0\left(\frac{\lambda_0}{\theta_0}\right) + \delta\lambda_0 = 2(-1.109) - 0.2014 = -2.4194,$$

$$\kappa_1 = \theta_0\left(\frac{\kappa_0}{\theta_0}\right) + \delta\kappa_1 = 2(0.861) - 0.0891 = +1.6329,$$

$$\theta_1 = 2 - 0.2546 = 1.7454.$$

α_1 is not given because it is better estimated from $\bar{y} - \theta_1 \sum \ln(1 - \xi_i)/n$ in the next iteration, as described above.

The rather large and approximately equal adjustments to λ_0 and θ_0 should be noted; the estimates of these parameters are in fact highly correlated and have relatively large variances; hence the reduction of the *S. S.* of residuals (from 0.0265 to 0.0239) following the adjustment is rather small.

A second iteration using the values α_1 , λ_1 , κ_1 , θ_1 gives

$$\delta\alpha_1 = -0.00446770, \qquad \alpha_2 = 8.5538,$$
$$\delta\lambda_1 = +0.02565976, \quad \text{and} \quad \lambda_2 = 2.3937,$$
$$\delta\kappa_1 = +0.00782844, \qquad \kappa_2 = 1.6407,$$
$$\delta\theta_1 = +0.02010622, \qquad \theta_2 = 1.7655.$$

and a third and final iteration gives

$$\alpha_3 = 8.5539,$$
$$\lambda_3 = 2.3917,$$
$$\kappa_3 = 1.6415,$$
$$\theta_3 = 1.7676$$

with dispersion matrix

$$\begin{bmatrix} 0.01419 & 0.02379 & 0.01526 & 0.06075 \\ & 0.13220 & 0.06751 & 0.21618 \\ & & 0.03705 & 0.11775 \\ & & & 0.40847 \end{bmatrix}.$$

In comparing the estimates and their variances and covariances with those obtained for θ assumed known and equal to 2, it should be remembered that the effective parameters estimated in the latter case were $\alpha/\vartheta = \alpha/2$ etc. Thus parameter values for the logistic case should be multiplied by 2 and their variances and covariances by 4 for comparison with those of the four-parameter curve. As was to be expected, the variances of $\hat{\alpha}$, $\hat{\lambda}$, and $\hat{\kappa}$ have been considerably increased by the inclusion of θ, also $\hat{\theta}$ itself is poorly determined with a standard error of ± 0.639, so that it does not differ significantly from the value of 2 originally used.

ALLOCATION OF SAMPLE POINTS

This section is concerned with the effect on the efficiency of estimation of different allocations of position of sample points on the curve. Obviously points on the curve where $x^{1/\theta}$ is small compared to $A^{1/\theta}$ give almost no information about A, while points where $x^{1/\theta}$ is close to $A^{1/\theta}$ give almost no information about λ and κ, the parameters defining the exponential part of growth. To reduce the range of possibilities of the distribution of the sample points to manageable proportions, attention will be confined to samples at points equally spaced with regard to t and symmetrically arranged about $\tau = 0$. [In practice, a rough idea of the values of the parameters will enable observations to be taken at times similar to those considered here]. The points of the arrangements considered are spaced along the t scale in units of τ or $\frac{1}{2}\tau$, while the ranges spanned are 6τ, 10τ, and 14τ. Table VII gives the relative sampling variances per point for the parameters, and also the generalized information per point using $|\ \mathbf{Q}\ |/n$ where n is the number of points and $\mathbf{Q}$ the information matrix for the samples. Two cases are considered: θ known (3 parameters to be estimated) and θ unknown (4 parameters to be estimated).

The table shows that more intensive sampling of a given range [e.g. $-3(\frac{1}{2})3$ instead of $-3(1)3$] slightly increases the sampling variance per point while increasing the information per point. The increased information implies that some or all of the correlations between the estimates have been reduced by the increased density of points, although the arrangement $3(\frac{1}{2})3$ is less efficient than $3(1)3$ when measured in terms of sampling variances only. Increasing the range reduces the sampling variances per point as one might expect, and so yields more information than more intensive sampling of the same range. The sampling variances of $\hat{\alpha}$, $\hat{\lambda}$, and $\hat{\kappa}$ are considerably increased when θ is unknown, particularly when the range of τ is small. This is of course a reflection of the fact that curves for neighbouring values of

TABLE VII

SAMPLING VARIANCES PER POINT OF THE PARAMETER ESTIMATES AND THE GENERALIZED INFORMATION PER POINT FOR VARIOUS DISTRIBUTIONS OF THE OBSERVATIONS

θ KNOWN, α, λ, κ UNKNOWN, $\sigma^2 = 1$

No. of points	Allocation of τ	Sampling variance per point			Generalized information per point
		$\hat{\alpha}$	$\hat{\lambda}$	$\hat{\kappa}$	
7	−3(1)3	5.39	39.2	3.60	1.57
11	−5(1)5	3.11	23.1	1.14	16.93
15	−7(1)7	2.59	18.5	0.56	73.16
13	−3($\frac{1}{2}$)3	6.05	42.9	4.21	4.32
21	−5($\frac{1}{2}$)5	3.22	23.8	1.25	54.80
29	−7($\frac{1}{2}$)7	2.63	18.8	0.60	252.6

α, λ, κ, θ UNKNOWN, $\sigma^2 = 1$

No. of points	Allocation of τ	Sampling variance per point				Generalized information per point
		$\hat{\alpha}$	$\hat{\lambda}$	$\hat{\kappa}$	$\hat{\theta}$	
7	−3(1)3	14.26	361.2	41.50	339.3	0.0324
11	−5(1)5	4.99	84.0	5.28	89.4	2.008
15	−7(1)7	3.50	53.4	1.62	54.4	20.16
13	−3($\frac{1}{2}$)3	17.20	420.8	51.57	398.4	0.2655
21	−5($\frac{1}{2}$)5	5.34	91.5	6.13	96.3	11.95
29	−7($\frac{1}{2}$)7	3.60	45.5	1.82	56.2	130.4

θ can be made to agree very closely over this range of τ by suitable changes in the other parameters. $\hat{\lambda}$ and $\hat{\theta}$ have the largest sampling variances in all the arrangements and hence are the most difficult to estimate accurately. For instance, if an individual value of w_i in an experiment had a percentage standard error of 5, then var y = var (ln w) $\sim$ 0.0025, so that with the allocation −3(1)3 we should have var $\hat{\theta}$ = 0.0025 × 48.47, whence s.e. $\hat{\theta}$ = ±0.35. Since θ is often in the range 1–2, the allocation τ = −3(1)3 would be inadequate to determine this parameter at all accurately. Similar considerations apply to $\hat{\lambda}$. By such arguments one can find what range w must cover if adequate estimates of the parameters are to be obtained for

$$W = A/(1 + e^{-\tau})^{\theta}$$

so that $\tau = \ln [W^{1/\theta}/(A^{1/\theta} - W^{1/\theta})] = \text{logit } (W/A)^{1/\theta}$. Thus if θ is, say, equal to 2 then $\tau = 3$ corresponds to $(W/A)^{1/\theta} = 0.95257$ whence $W/A = 0.976$; similarly $\tau = -3$ gives $W/A = 0.024$. Thus when $\theta = 2$ the range $\tau = -3$ to 3 implies that W ranges from 2.4 to 97.6 percent of A, and the argument above shows that this range will often be insufficient for adequate estimates of some of the parameters. Note that the larger the value of θ the greater the range of W/A required to cover the same range of τ.

DISCUSSION

This paper is not the place for a discussion of the place of mathematical functions in the description and analysis of growth. A great deal has been written on the subject both for and against the utility of this approach, and it suffices to say that I assume in this paper that differential equations and their associated integrals *have* some usefulness, and that methods are required for the efficient estimation of the parameters. For an approach to the problem of interpreting growth curves which involves replacing chronological time t by some function of meteorological observations see Nelder *et al.* [1960]. [In the example above t is in fact a scale based on total incoming radiation].

The method of estimation used in this paper is based on three assumptions: (i) that the w_i are independent, (ii) that $E(y_i) = Y_i$ and (iii) that var y_i is independent of Y_i. It may reasonably be asked how suitable the procedure is likely to be if some or all of the assumptions are not true, and this involves us in an analysis of the errors in the Y_i. Errors may be due to variation in the parameters from one individual to another, for either genetic or non-genetic reasons; or they may arise from errors in t_i, caused by using the wrong time-scale. In addition we have the possibility of systematic errors arising from deviations from the form of the curve actually used in the fitting. It will certainly not be exactly true that if, for instance, κ has a normal distribution in the population of individuals whose growth is being studied, then random sampling will enable us to set $E(y_i) = Y_i$, where Y_i is given by (3) with the mean of κ used in the formula. But such biases will not be serious if the variance of κ is small, i.e. if we control the genetic and environmental uniformity of the population well. If the w_i are from the same experimental units throughout, which is the commonest cause of non-independence, the method will remain satisfactory if var (y_i) remains constant, where the variance is now measured *within* individual growth curves. However sampling variances of the estimates of parameters must now be calculated from the variation in the parameter values *between* individuals. If the variation between indi-

vidual curves is much greater than the variation within them, then the efficiency of the fitting method becomes correspondingly less important, and even graphical methods might suffice. A frequent cause of deviations of var (y_i) from constancy is the occurrence of constant-variance weighing errors on the w scale. On the log. scale these become more serious as the weight falls, and lead to var (y_i) increasing rapidly at very low values of w, where the weights are not large compared to the weighing errors. Difficulties in measuring very small distances on a plant cause the same effect. In practice the change in var (y) can often be approximately eliminated by a suitable increase in replication at very low levels of w.

The model employed here for fitting the logistic curve may be contrasted with a method suggested by Stevens [1951], who proposed writing it in the form

$$\frac{1}{W} = \frac{1}{A}(1 + \beta e^{-\kappa t})$$

and using his method for fitting curves of the type

$$z = \alpha + \beta\rho^t, \quad \text{with} \quad z = \frac{1}{W}, \quad \text{and} \quad \rho = e^{-\kappa}.$$

Since he gave equal weight to his z's in the fitting, this is equivalent to assuming that $1/w$ has constant variance and hence that var $(\ln w) \propto W^2$ to the first order. Though conditions may exist where var $(\ln w) \propto W^2$, in my experience it is usually much closer to the truth to take var $(\ln w)$ constant. Several papers concerned with fitting the curve $z = \alpha + \beta\rho^t$ have appeared (e.g. Nair [1954], Patterson [1956], Finney [1958], Patterson and Lipton [1959]), but these are almost entirely concerned with the case where z has constant variance and where the t_i are equally spaced. Where time scales based on meteorological measurements (such as day-degrees) are used for field crops, it is usually impossible or impracticable to arrange for equally spaced t's, so that methods used in the above mentioned papers are no longer available, even if it could be assumed that var z was constant. In addition, none of the methods is immediately applicable to the general case where θ has to be estimated.

The reasons behind the particular choice of the parameters in (3) should perhaps be mentioned. There are, of course, an infinite number of equivalent ways of writing (3), in so far as the structural parameters are concerned. The particular form used has been chosen to reduce the computing labour of the iterative solution as much as possible, while retaining a set of parameters with fairly clear meanings as far

as growth is concerned. Thus α = ln (asymptotic value of W), while λ and κ define the exponential growth stage for large negative t when $W \sim Ae^{\lambda+\kappa t}$. A possible interpretation of θ for a field crop in terms of the spatial distribution of plant material has been given by Nelder *et al.* [1960]. The form used may be capable of further improvement, especially from the point of view of the convergence of the iterative process. It is an interesting point to what extent approximately orthogonal parameters can be found for the general non-linear function, that is parameters such that the cross terms in the dispersion matrix are small compared to the diagonal terms, and whether the use of such parameters would speed the convergence of the iterative process. While a linear transformation of the parameters leads to equivalent iterative equations, non-linear transformations in general do not, and possibly the speed of convergence would be affected by the particular specification of the parameters.

A natural extension of the generalized logistic equation as defined here is the five-parameter equation $dW/dt = \alpha W^{\xi} - \beta W^{\eta}$ discussed by von Bertalanffy [1957]. The estimation of the parameters of this equation, subject to the same assumptions as those considered above, is greatly complicated by the lack of any general explicit solution of the equation. Consequently expected values would have to be computed by numerical integration which makes the labour involved excessive except to those having electronic computers available. A general method for the fitting of differential equations has been given by Box [1956], and this could be applied to the general equation. However we may expect that the introduction of the fifth parameter would entail the existence of very extensive data if reasonably accurate estimates of the parameters were to be obtained. The data discussed above cover a 380-fold range of weights, and the standard error of a single weight was about 5.5 percent, yet the s.e. of $\hat{\theta}$ was as high as ± 0.64. The introduction of the fifth parameter might well require a much larger range of weights to give reasonably accurate estimates. One consequence of this situation is that it becomes difficult to test models based on *a priori* values of the exponents ξ and η, unless very extensive data are available, since the fits of curves having ξ and η differing quite widely from the *a priori* values would be hardly distinguishable.

SUMMARY

The least-squares fit of the curves defined by

$$\frac{dW}{dt} = \kappa W\left[1 - \left(\frac{W}{A}\right)^{1/\theta}\right]$$

is derived for the case when the sample values of ln W are independent, unbiased, and of constant variance.

Tables are provided to assist the computing of the iterative process used for estimation, and a method is given for obtaining starting values for the parameters.

Evaluation of the sampling variances of the estimates of the parameters and the generalized information shows that the range which the observations cover is more important than the density of sample points within that range if minimum sampling variance or maximum information per point is required. The introduction of θ as an unknown increases the sampling variances of the other parameters, the increase being especially marked when the range of $(W/A)^{1/\theta}$ is small.

Some possible sources and consequences of deviations from the assumptions underlying the fitting are discussed, and also the difficulties involved in extending the fitting to the curves defined by

$$dW/dt = \alpha W^{\xi} - \beta W^{\eta}.$$

It is stressed that sensitive tests of hypotheses involving *a priori* values of parameters may demand very extensive data.

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COMBINED ANALYSIS OF BALANCED INCOMPLETE BLOCK DESIGNS WITH SOME COMMON TREATMENTS

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INTRODUCTION

On many occasions, research workers have to lay out their experiments at different places with one or more treatments common to each experiment. The reason may be the lack of sufficient space at one location as in field experiments, or as in industrial problems the availability of only a limited number of experimental units with stipulated conditions with the result that the experiment has to be laid out at different plants. In either case, the research workers are interested in the combined analysis of the data from all of the experiments, besides their individual analyses. The purpose of the present paper is to suggest a simplified method to obtain adjusted treatment components for the combined analysis when the individual experiments are laid out in balanced incomplete block (BIB) designs. Gomes and Guimares [1958] have considered the case when the individual experiments are laid out in randomised complete block designs. The case dealt with by Gomes and Guimares could be deduced as a special case from general method suggested in this paper.

NATURE OF THE PROBLEM

Suppose there are g BIB experiments to be analysed jointly with the following parameters:

v = number of treatments,
b = number of blocks,
r = number of replications for each treatment,
k = number of units per block,
λ = number of times any two treatments occur together in the design.

Let us suppose that, for each experiment, there are c treatments common. Hence, there are $c + g(v - c)$ different treatments in all. Let us, following Gomes and Guimares, call the c treatments (common to all

experiments) 'common' treatments and the rest, $g(v - c)$ treatments, 'regular' treatments. Hence, the combined experiment will have for its parameters

$v' = c + g(v - c), \quad b' = gb, \quad k' = k,$

$r' = gr$ for the common treatments,
r for the regular treatments,

$\lambda' = g\lambda$ for two common treatments,
λ for a common and a regular treatment from the same experiment,
0 for two regular treatments from two different experiments.

As one can see, the design is no longer a balanced one, but still possesses the property of connectedness.

METHODS OF OBTAINING ADJUSTED TREATMENT SUM OF SQUARES

We proceed to find the adjusted treatment sum of squares for the combined analysis by two methods. The general method suggested by C. R. Rao [1947] treats the combined data as that of a new incomplete block experiment. Here we will only outline this method since it is well known in the statistical literature. The simplified method, which the author would like to introduce, makes use of the individual analyses already performed and this will be given later, along with the results for various special cases.

Classical Method

Here, the whole problem of combined analysis reduces to the solution of the adjusted normal equations

$$\mathbf{Ct} = \mathbf{Q} \tag{1}$$

where the matrix $\mathbf{C}$ $(v' \times v')$ and the column vectors $\mathbf{t}$ $(v' \times 1)$, $\mathbf{Q}$ $(v' \times 1)$ have usual meanings. The elements of the $\mathbf{C}$ matrix are

$c_{ii} = g\lambda(v - 1)/k$ for common treatments,
$c_{ij} = -\lambda g/k$ for any two common treatments,
$c_{ii} = \lambda(v - 1)/k$ for regular treatments,
$c_{ij} = -\lambda/k$ for any two regular treatments from the same experiment,
$c_{ij} = 0$ for any two regular treatments from different experiments.

Here the rank of the $\mathbf{C}$ matrix is $v' - 1$ and hence we adopt a suitable

restriction, so that it becomes non-singular and easy to invert. We use the restriction

$$\frac{\lambda g}{k}(t_1 + t_2 + \cdots + t_c) + \frac{\lambda}{k}\sum_{i=c+1}^{g(v-c)} t_i = 0.$$

By using this restriction, the **C** matrix reduces to

$$\begin{bmatrix} Erg\ \mathbf{I}_1 & \mathbf{0} \\ -\frac{\lambda}{k}\mathbf{J}_1 & \mathbf{I}_3 \times \left(Er\ \mathbf{I}_2 - \frac{\lambda}{k}\mathbf{J}_2\right) \end{bmatrix}$$

where **I** is the identity matrix, **0** is a matrix having only zero elements, **J** is a matrix having only unity elements, $\times$ indicates the direct product and E is the efficiency factor of the BIB design; the dimensions of the matrices are

$$\begin{aligned} I_1 &= ec \times c, \qquad I_2 = (v-c) \times (v-c), \\ I_3 &= g \times g, \qquad J_1 = g(v-c) \times c, \\ J_2 &= (v-c) \times (v-c), \qquad 0 = c \times g(v-c). \end{aligned} \tag{2}$$

This matrix has a pattern discussed by Roy in one of his papers (3) and hence the inverse can be easily found. The inverse turns out to be

$$\begin{bmatrix} \frac{1}{Erg}\mathbf{I}_1 & \mathbf{0} \\ \frac{1}{gErc}\mathbf{J}_1 & \mathbf{I}_3 \times \left(\frac{1}{Er}\mathbf{I}_2 + \frac{1}{Erc}\mathbf{J}_2\right) \end{bmatrix}$$

where $\mathbf{I}_1$, $\mathbf{I}_2$, $\mathbf{I}_3$, $\mathbf{J}_1$, $\mathbf{J}_2$, $\mathbf{0}$ are of the same dimensions as in (2). Hence, the solution of (1) turns out to be

$$\hat{\mathbf{t}} = \mathbf{C}^{-1}\mathbf{Q}. \tag{3}$$

Finally, the adjusted treatment sum of squares is $\hat{\mathbf{t}}'\mathbf{Q}$ where $\hat{\mathbf{t}}'$ $(1 \times v')$, a row vector. Total and Blocks (unadj) sums of squares are found in usual manner.

Simplified method:

This method is useful to those research workers who are not conversant with matrix algebra and advanced mathematical topics. The method suggested here is based on individual analyses of g BIB experiments.

Suppose we have performed individual analyses of g BIB experiments with the same parameter values, viz. v, b, r, k, λ and with c common treatments.

Let

$Q_{i.s}$ = adjusted treatment total of the ith common treatment in sth experiment,
$i = 1, \cdots, c$,
$s = 1, \cdots, g$,

$Q_{i.}$ = $\sum_{s=1}^{g} Q_{i.s}$ = adjusted treatment total for ith common treatment in combined analysis, $i = 1, \cdots, c$,

$Q_j^{(s)}$ = adjusted treatment total for jth regular treatment in sth experiment, $j = 1, \cdots, (v - c)$, $s = 1, \cdots, g$.

From these values, we obtain adjusted treatment sum of squares as follows.

Form the following two-way table, Table I.

TABLE I

TWO-WAY TABLE OF COMMON TREATMENTS AND EXPERIMENTS WITH $Q_{i.s}$ VALUES

Expts.	c. treat				Total
	i_1	i_2	...	i_c	
E_1	$Q_{1.1}$	$Q_{2.1}$	...	$Q_{c.1}$	$Q_{..1}$
E_2	$Q_{1.2}$	$Q_{2.2}$	...	$Q_{c.2}$	$Q_{..2}$
...	...	...	...	...	...
E_g	$Q_{1.g}$	$Q_{2.g}$	...	$Q_{c.g}$	$Q_{..g}$
Total		Q_2	...	Q_c	$Q_{..}$

Here

$$Q_{..} = \sum_{i=1}^{c} Q_{i.} ,$$

$$Q_{i} = \sum_{s=1}^{g} Q_{i.s} ,$$

and

$$Q_{..} = \sum_{i=1}^{c} \sum_{s=1}^{g} Q_{i.s} .$$

Obtain (common treatments × experiments) interaction in the usual way. Then,

the adjusted treatment sum of squares for the combined analysis is

Adj. Treat. S.S. (Combined Analysis) = Sum of Adj. Treat. S.S. from each exp.

$$-1/Er \text{ (Common Treat. } \times \text{ Exp. Interaction)} \tag{4}$$

ESTIMATION OF TREATMENT ESTIMATES AND VARIANCES OF TREATMENT DIFFERENCES FOR VARIOUS CASES

Using the notation at the beginning of this section, we have

$$\hat{t}_i = Q_i/gEr, \tag{5}$$

$$\hat{t}_i^{(s)} = \frac{1}{Er}\left[Q_i^{(s)} + \frac{1}{c}\sum_{j=1}^{v-c} Q_i^{(s)} + \frac{1}{cg}\sum_{i=1}^{c} Q_i\right]. \tag{6}$$

Further note that, if $t_i'^{(s)}$ is the estimate of the jth regular treatment only using information from the sth experiment and if $t'_{i,s}$ has a similar meaning for the ith common treatment, then

$$\hat{t}_i = \frac{1}{g}\sum_{s=1}^{g} t'_{i,s}\,, \tag{7}$$

$$\hat{t}_i^{(s)} = t_i'^{(s)} + \frac{1}{c}\sum_{j=1}^{v-c} t_i'^{(s)} + \frac{1}{g}\sum_{i=1}^{c} \hat{t}_i\,, \tag{8}$$

or

$$\hat{t}_i^{(s)} = t_i'^{(s)} - \frac{1}{c}\sum_{i=1}^{c} t'_{i,s} + \frac{1}{g}\sum_{i=1}^{c} \hat{t}_i\,. \tag{8a}$$

Thus to find the best estimates, one need only estimate the treatments for each experiment seperately and use (7) and (8) or (8a) to obtain the final estimates. Formulae (8) and (8a) could be used with advantage when $(v - c) < c$ and $(v - c) > c$, respectively.

At this stage, it might be noted that the adjusted treatment sums of squares may also be obtained by the following alternative formula:

$$\text{Adjusted treatment S.S.} = \sum_{i=1}^{c} \hat{t}Q_i + \sum_{s=1}^{g}\sum_{j=1}^{v-c} \hat{t}_i^{(s)}Q_i^{(s)}. \tag{9}$$

The variances of the various treatment differences are obtained as follows:

(1) For treatment estimates $\hat{t}_i$, $\hat{t}_{i'}$ belonging to the common group

$$V_1 = \text{var}\,(\hat{t}_i - \hat{t}_{i'}) = 2s^2/gEr.$$

(2) For treatment estimates $\hat{t}_i$ and $\hat{t}_j^{(s)}$ where $\hat{t}_i$ is from common group and $\hat{t}_j$ is from regular group.

$$V_2 = \text{var}\,(\hat{t}_i - \hat{t}_j^{(s)}) = \left\{\frac{1}{rE}\left[1 + \frac{1}{g} + \frac{1}{c} - \frac{1}{cg}\right]s^2\right\}.$$

(3) For treatment estimates $\hat{t}_i^{(s)}$ and $\hat{t}_{i'}^{(s)}$ where both of them belong to the regular group of the same experiment

$$\hat{V}_3 = \text{var}\,(\hat{t}_i^{(s)} - \hat{t}_{i'}^{(s)}) = 2s^2/rE.$$

(4) For treatment estimates $t_i^{(s)}$ and $t_{i'}^{(s')}$ where both of them belong to the regular group but are from different experiments

$$\hat{V}_4 = \text{var}\,(\hat{t}_i^{(s)} - \hat{t}_i^{(s')}) = \frac{2}{rE}\left(1 + \frac{1}{c}\right)s^2.$$

s^2 in all of the above formulae stands for the estimated error variance.

SPECIAL CASES

(a) There may be several BIB experiments with only one treatment common which might be a control. In this case $c = 1$.

Let t_1 denote the control. Then we have the following results.

I. *Adjusted treatment S. S.*

Sum of the adjusted treatment sums of squares from individual analyses

II. *Treatment estimates.*

$$\hat{t}_1 = \frac{1}{g}\sum_{s=1}^{g} t'_{1.s}\,,$$

$$\hat{t}_i^{(s)} = t_i'^{(s)} - t'_{1.s} + \frac{1}{g}\hat{t}_1 \quad \text{based on (8a).}$$

III. *The variances of treatment differences.*

(1) This case does not arise

(2) $\hat{V}(\hat{t}_1 - \hat{t}_i^{(s)}) = 2s^2/rE.$

(3) $\hat{V}(\hat{t}_i^{(s)} - \hat{t}_{i'}^{(s)}) = 2s^2/rE.$

(4) $\hat{V}(\hat{t}_i^{(s)} - \hat{t}_i^{(s')}) = 4s^2/rE.$

The numbers here correspond to those in the preceding section.

(b) There may be several BIB experiments with the same treatments. In this case $c = v$. In other words, we want to combine several BIB experiments with identical parameter values and treatments, conducted at different places. In this case, we have results as follow:

I. *Adjusted treatments S.S.*

$$\frac{1}{rEg}\sum_{i=1}^{v} Q_i^2 .$$

II. *Treatment estimates.*

$$\hat{t}_i = \frac{1}{g}\sum_{s=1}^{g} t'_{i.s} \qquad i = 1, \cdots, c(=v).$$

III. *The variances of treatment differences.*

(1) $\quad \mathrm{var}\,(\hat{t}_i - \hat{t}_{i'}) = 2s^2/rEg, \qquad i \neq i', \qquad i, i' = 1 \cdots, v.$

(2), (3), (4) These cases do not arise.

(c) The most important special case is obtained when $b = r = \lambda$ and $k = v$. In this case BIB designs reduce to well known randomised complete block designs with c common treatments. The simplified analysis will remain the same with corresponding substitution.

(d) Cases (a) and (b) can be considered for (c).
Since (c) and (d) have been considered in detail by Gomes *et al* [1958], they will not be repeated here. However, we present the adjusted treatment sums of squares for the three situations since they are somewhat simpler than those given before.

Case (i), $c = 1$.

Adjusted treatment S. S. = Sum of treatment S. S. from the individual experiments.

Case (ii), $1 < c < v$.

Adjusted treatment S. S. = $\left\{\begin{matrix}\text{Sum of treatment S. S. from} \\ \text{the individual experiments}\end{matrix}\right\}$ −

{Interaction (common treatment × experiments) using treatment totals.}

Case (iii), $c = v$.

Treatment S. S. $= \sum_{i=1}^{v} \frac{T_i^2}{rg} - \frac{G^2}{gvr}$

where T_i is the total for the ith treatment over all experiments and G is the grand total for all experiments.

EXAMPLE

(Hypothetical problem purely to illustrate the procedure)

Two BIB experiments with the following parameter values are conducted and the combined analysis is required. The parameter values are

$v = 7, \quad b = 7, \quad r = 4, \quad k = 4, \quad \lambda = 2, \quad g = 2$ and $c = 3$.

The following data are at our disposal.

TABLE 2

ANALYSIS OF VARIANCE FOR THE INDIVIDUAL EXPERIMENTS

	Experiment 1		Experiment 2	
Source	d.f.	S.S.	d.f.	S.S.
Blocks (unadjusted)	6	342.71	6	63.21
Treatments (adjusted)	6	171.14	6	154.50
Residual	15	165.11	15	469.00

$Q_{1,1} = 18.00, \quad Q_4^{(1)} = -1.00, \quad Q_{1,2} = 13.75, \quad Q_8^{(2)} = 4.50,$

$Q_{2,1} = 7.50, \quad Q_5^{(1)} = -9.75, \quad Q_{2,2} = -5.75, \quad Q_9^{(2)} = 0.50,$

$Q_{3,1} = -6.75, \quad Q_6^{(1)} = -8.75, \quad Q_{3,2} = -9.75, \quad Q_{10}^{(2)} = -8.25,$

$Q_7^{(1)} = 0.75. \qquad Q_{11}^{(2)} = -5.00.$

Form, with $Q_{i,.}$ values, the following two-way table.

	t_1	t_2	t_3	Total
E_1	18.00	7.50	−6.75	18.75
E_2	13.75	−5.75	−9.75	−1.75
Total	31.75	1.75	−16.50	17.00

The (common treatment × experiments) interaction is found to be 31.2708.

Hence

Treatment (adjusted) S. S. for the combined analysis

$= 171.14 + 154.50 - 4/2 \times 7\ (31.2708)$

$= 316.7055$

The combined analysis is given below.

TABLE 3

COMBINED ANALYSIS OF VARIANCE

Source of variation	d.f.	S.S.	M.S.
Blocks (unadjusted)	13	425.375	32.7212
Treatments (adjusted)	10	316.708	31.6708
Residual	32	643.042	20.0951

With the use of the equations (7) and (8) we obtain the following treatment estimates for the combined analysis:

$$\hat{t}_1 = 4.5357, \quad \hat{t}_2 = 0.2500, \quad \hat{t}_3 = -2.3571,$$
$$\hat{t}_4^{(1)} = -1.2619, \quad \hat{t}_5^{(1)} = -3.7619, \quad \hat{t}_6^{(1)} = -3.4762,$$
$$\hat{t}_7^{(1)} = -0.7619, \quad \hat{t}_8^{(2)} = 2.2619, \quad \hat{t}_9^{(2)} = 3.9762,$$
$$\hat{t}_{10}^{(2)} = -1.3810, \quad \hat{t}_{11}^{(2)} = -0.4524.$$

Variances of treatment differences are

$$\hat{V}_1 = 2s^2/Erg = 5.741,$$
$$\hat{V}_2 = \frac{1}{Er}\left[1 + \frac{1}{g} + \frac{1}{c} - \frac{1}{cg}\right]s^2 = 9.569,$$
$$\hat{V}_3 = 2s^2/Er = 22.966,$$
$$\hat{V}_4 = \frac{2}{Er}\left(1 + \frac{1}{c}\right)s^2 = 15.310.$$

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GENERALIZED ASYMPTOTIC REGRESSION AND NON-LINEAR PATH ANALYSIS[1]

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1. INTRODUCTION

It is a fundamental fact of statistical inference that the information contained in an analysis of experimental data is the sum of the a priori information built into the statistical model employed and the a posteriori information contained in the data itself. For this reason the biometrician must be concerned not only with the efficiency of his estimation procedures but also with the adequacy of his descriptive model. Much care must be taken to ensure that all relevant a priori information is utilized in the construction of the model. In some cases it is possible to derive rather sophisticated theoretical models on the basis of acquired knowledge and intelligent hypothesizing. These models are often conveniently found as solutions of differential equations. In other cases little more may be known than that the biological process in question is continuous. In this latter case one may resort to polynomial models where the degree of the polynomial is either found empirically or by prior consideration of the number of "bends" which one can reasonably assume to take place in the process being studied. In certain other cases it may be known that the process approaches some asymptotic value. This is especially true in those cases known as "growth" processes. The general ineptness of polynomial models for purposes of describing such asymptotic situations has been repeatedly pointed out, although polynomials in the reciprocals may sometimes be used conveniently.

Stevens [1951] and Pimentel-Gomes [1953], writing in this journal, have discussed inferential methods related to one form of transcendental asymptotic model, the so-called exponential model,

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$$y = \alpha + \beta e^{-x/\gamma} + \epsilon, \tag{1}$$

where x and y are observables; α, β and γ are unknown parameters to be estimated; and ϵ is a random error. The above mentioned writers give convenient computational procedures for finding maximum likelihood estimates when ϵ has a normal distribution with constant variance and the errors are uncorrelated one with another. Even when the errors are non-normal these same methods provide least square estimates of the parameters. The numerical devices used for finding the estimates are based on methods devised by Gauss and described in detail in the books by Whitaker and Robinson [1944] and Deming [1943]. The method of estimation, maximum likelihood, is due originally to Gauss and is discussed extensively by Fisher [1956] who is mainly responsible for our knowledge of the properties of the method. Both the numerical devices and the estimation method are reviewed in the recent work by Williams [1959].

Asymptotic models fall conveniently into either the class of transcendental models, including the exponential, or the class of rational models, including models such as the rectangular hyperbola and the inverse square law.

This paper considers the general class of rational models and a special sub-class of transcendental models that may be regarded as a generalization of the exponential model. Appropriate techniques for estimation and for determination of asymptotic confidence limits, similar to those given by Stevens for the exponential, are provided. An alternative "parabolic method" of constructing confidence limits, valid for small samples, is also given.

In many practical biological situations a number of variables are related one with another in complex causal networks. Wright [1918, 1921] devised methods, which he termed path analysis, for analysizing such networks when the relationships between the variables are linear. Turner and Stevens [1959] have reviewed these methods for the important case when some of the primary variables may be "fixed" or without probability distributions. The present paper considers some aspects of such situations when the relationships between variables are of the transcendental variety rather than linear.

All of the models considered in this paper are non-linear in some of the unknown parameters. This implies that sufficient estimates and hence fiducial limits are not available.

In addition the maximum likelihood estimates, though consistent and efficient, will be generally biassed, will not have normal distributions for small samples and will generally not have explicit forms, thus

requiring iterative solution methods. This is the price one has to pay for more adequate symbolic description of the process being studied. The gain in meaningfullness is generally well worth even this heavy toll.

2. RATIONAL REGRESSION

Let us denote a particular p-th degree polynomial by $P_p(x)$ and a particular q-th degree polynomial by $Q_q(x)$ and then let us consider the regression model arising from the rational function,

$$y = [P_p(x)/Q_q(x)] + \epsilon, \tag{2}$$

where again x and y are observables and ϵ is a random error assumed to have a normal distribution with zero expectation and constant variance σ^2. The errors are also assumed to be uncorrelated one with another and with the values of x. At least some of the coefficients in the polynomials are unknown parameters to be estimated.

The numerical device for estimation due to Gauss, which was alluded to in the previous section, involves expansion of $y - \epsilon$ about "trial values" of the unknown parameters in a Taylor's series. The method is sketched in Section 4 and is there applied to the models discussed in Section 3. However, a simpler approach is available for the rational model (2).

Suppose that $Q_q(x) = 1 + \beta_1 x + \cdots + \beta_q x^q$, so that (2) may be written: $y = [P_p(x)/(1 + \beta_1 x + \cdots + \beta_q x^q)] + \epsilon$. If we multiply through by $Q_q(x)$ and rearrange we get

$$y = P_p(x) - \beta_1 xy - \cdots - \beta_q x^q y + Q\epsilon. \tag{3}$$

Now (3) is an ordinary multiple linear regression model except for the factor Q in the error term. Thus weighted least squares could be used for estimating the unknown parameters if the weights Q^{-2} were known. A simple plan is to take trial values for the parameters $\beta_1, \cdots, \beta_q$ and compute provisional weights. Then (3) is fitted by least squares giving better estimates of the β's as well as provisional estimates for $\alpha_0, \alpha_1, \cdots, \alpha_p$ occurring in $P_p(x)$. Using the improved estimates for the β's, better weights are determined and the fitting is repeated. The process is thus iterated through several cycles until stable values of the estimates are obtained. In many cases it is sufficient to use constant weights ($Q^{-2} = 1$) in the first cycle of iteration, thus not requiring trial values.

Asymptotic variances and confidence limits are found in the usual way from the final least square fit. Thus if for n observations we have

$$\mathbf{X} = \begin{bmatrix} 1 & x_1 & x_1^2 & \cdots & x_1^p & x_1y_1 & x_1^2y_1 & \cdots & x_1^qy_1 \\ 1 & x_2 & x_2^2 & \cdots & x_2^p & x_2y_2 & x_2^2y_2 & \cdots & x_2^qy_1 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 1 & x_n & x_n^2 & \cdots & x_n^p & x_ny_n & x_n^2y_n & \cdots & x_n^qy_1 \end{bmatrix},$$

$$\mathbf{B}' = (\alpha_0\ \alpha_1\ \cdots\ \alpha_p\ \beta_1\ \cdots\ \beta_q),$$

$$\mathbf{Y}' = (y_1\ y_2\ \cdots\ y_n),$$

$$\mathbf{W} = \begin{bmatrix} Q_1^{-2} & 0 & \cdots & 0 \\ 0 & Q_2^{-2} & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & Q_n^{-2} \end{bmatrix},$$

then the final estimates after iterating are

$$\hat{\mathbf{B}} = (\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}\mathbf{X}'\mathbf{W}\mathbf{Y} \tag{4}$$

and the asymptotic variances and covariances are given by

$$\text{Cov}\,(\hat{\mathbf{B}}) = (\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}s^2, \tag{5}$$

where s^2, the estimate of σ^2, is provided by

$$s^2 = (\mathbf{Y}'\mathbf{W}\mathbf{Y} - \hat{\mathbf{B}}'\mathbf{X}'\mathbf{W}\mathbf{Y})/(n - p - q - 1). \tag{6}$$

If the error in (2) depends upon x in a known way, only a slight modification of the procedure is required. Suppose that $\epsilon_x = f(x)\cdot\epsilon$. Then the error term in (3) will be $fQ\epsilon$ and the weight matrix $\mathbf{W}$ will be diagonal with elements $(f_iQ_i)^{-2}$ instead of $(Q_i)^{-2}$. Formulas (4), (5), and (6) will remain the same.

Computational details for those not familiar with linear regression methods are given by Williams [1959]. Let the elements of $(\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}$ be denoted by c_{ij} ; then the individual asymptotic confidence limits for each coefficient are

$$\begin{aligned} \hat{\alpha}_i - t_\pi\sqrt{c_{ii}s^2} \le \alpha_i \le \hat{\alpha}_i + t_\pi\sqrt{c_{ii}s^2}; \qquad & i = 0, 1, \cdots, p, \\ \hat{\beta}_i - t_\pi\sqrt{c_{ii}s^2} \le \beta_i \le \hat{\beta}_i + t_\pi\sqrt{c_{ii}s^2}; \qquad & i = 1, 2, \cdots, q, \end{aligned} \tag{7}$$

where t_π is a Student's t at an assigned confidence level $(1 - \pi)$ with $n - p - q - 1$ degrees of freedom.

As an example consider the case of $p = 0$ and $q = 1$, the case of the rectangular hyperbola. We have

$$y = [\alpha_0/(1 + \beta_1x)] + \epsilon \tag{8}$$

with asymptotes $x = -1/\beta_1$ and $y = 0$. Corresponding to (3) we have the regression equation $y = \alpha_0 - \beta_1xy + Q\epsilon$, where $Q = 1 + \beta_1x$.

A graphical estimate of the slope $-\beta_1$ can be obtained by plotting y against xy and provisional weights computed from $w = (1 + \beta_1 x)^{-2}$. Then using these provisional weights we compute

$$\hat{\beta}_1 = -\frac{\sum w \sum wxy^2 - \sum wxy \sum w}{\sum w \sum wx^2y^2 - (\sum wxy)^2} = -\frac{\sum w S_{xyy}}{\sum w S_{xxyy}} \tag{9}$$

and obtain better estimates of the weights. After stability is reached we find

$$\hat{\alpha}_0 = (\sum wy + \hat{\beta}_1 \sum wxy)/\sum w \tag{10}$$

and the estimate of the variance σ^2,

$$s^2 = \frac{1}{n-2}\left\{\frac{\sum w \sum wy^2 - (\sum wy)^2}{\sum w} - \frac{S_{xyy}^2}{S_{xxyy}}\right\}. \tag{11}$$

We also obtain estimates of the asymptotic variances for a_0 and b_1 :

$$\begin{aligned} s_{a_0}^2 &= s^2\left\{\frac{1}{\sum w} + \frac{(\sum wxy)^2}{(\sum w)^2 S_{xxyy}}\right\} \\ s_{b_1}^2 &= s^2/S_{xxyy} \end{aligned} \tag{12}$$

from which asymptotic confidence limits may be calculated.

3. TRANSCENDENTAL REGRESSION: THE SINGLE PROCESS LAW

The rational models discussed in the previous section may often be used to conveniently describe an asymptotic process. However, when more than just a few terms in the polynomials are required for adequate description of the process, the rational models may suffer from three deficiencies: (1) physical or biological meaning of the coefficients may be lost, (2) annoying "bumps" tend to appear in the fitted curve which have no reality in the actual process, and (3) excessive numerical computation may be required due to the number of parameters which need to be estimated.

Certain transcendental models may provide a more parsimonious description of an asymptotic process and yet preserve considerable flexibility of form. By "parsimony" is meant the ability to describe adequately with a small number of parameters. This may be accomplished by supplying the a priori information that the curve is regular in some way or another. For example, we may specify that the curve is monotonically increasing or decreasing throughout its course or that certain of the derivatives have this monotonicity property. We may then avoid the undesired "bumps" and make possible simpler com-

putations by using this information. In addition, since solutions of most differential equations are in terms of transcendental functions, we may wish to seek a model which is related to a class of differential equations, thus making interpretation of the parameters more meaningful.

One simple class of transcendental regression models has been called by Turner [1959] the *single process law*. Consider the differential equation

$$d\eta/d\xi = \delta(\eta - \alpha)/(\xi - \gamma\ \delta). \tag{13}$$

Integrating we get

$$\eta = \alpha + \beta(\xi - \gamma\ \delta)^{\delta}, \tag{14}$$

or

$$\eta = \alpha + \beta(\xi - \mu)^{\delta}, \qquad \mu = \gamma\ \delta.$$

Now let us suppose that the observables x and y are defined by the error equations $x = \xi$, and $y = \eta + \epsilon$, where ϵ is a random error defined as before. Thus the model corresponding to the single process law (14) is

$$y = \alpha + \beta(x - \gamma\ \delta)^{\delta} + \epsilon. \tag{15}$$

For convenience we will always take $x - \gamma\delta > 0$.

The proportionality constant δ in (13) determines the nature of the process. When δ is a positive integer, we have a polynomial process; however, the model (15) is non-linear when this integer is greater than two. When δ is a negative integer, then we have a rational process, a special case of the processes studied in the previous section. When δ is non-integral, the process is transcendental. In particular, when δ approaches infinity, either positively or negatively, the model (15) approaches the exponential model (1), $y = \alpha + \beta e^{-x/\gamma} + \epsilon$.

An interesting series of models, most of which are commonly used in curve fitting, is obtained when $2/\delta = -4, -3, -2, -1, 0, +1, +2$. These cases correspond to the *inverse square root law*, the *inverse two-thirds law*, the *rectangular hyperbola*, the *inverse square law*, the *exponential*, the *parabola*, and the *straight line*, respectively. Thus all of these are special cases of a continuously varying family of curves (See Figure 1). We observe that when $2/\delta$ is negative the curves have two asymptotes, that when $2/\delta = 0$ there is but one asymptote, and that when $2/\delta$ is positive there is no asymptote. Thus the exponential may be thought of as a "transition" curve between those curves possessing two asymptotes and those possessing none. Without loss of generality we may consider only the case of decreasing curves, commonly referred to as "extinction curves". Several useful constants for the

TABLE 1

CONSTANTS FOR SPECIAL EXTINCTION CURVES[a]

δ^{-1}	Name of Curve	δ	β	γ	Asymptote	Initial level	ξ^{b}_{25}	ξ_{50} "half-life"	ξ_{75}	ξ^{c}_{100} "point of extinction"	$\lambda^{d} = \xi_{75}/\xi_{50}$	Initial Velocity
1.0	Straight Line	1	<0	>0	—	$-\beta\gamma$	$\gamma/4$	$\gamma/2$	$3\gamma/4$	γ	1.5	β
.5	Parabola	2	>0	>0	—	$4\beta\gamma^2$	$(2-\sqrt{3})\gamma$	$(2-\sqrt{2})\gamma$	γ	2γ	1.7071	$-4\beta\gamma$
0	Exponential	∞	>0	>0	—	β	$\left(\log\frac{4}{3}\right)\gamma$	$(\log 2)\gamma$	$(\log 4)\gamma$	—	2.0	$-\frac{\beta}{\gamma}$
$-.5$	Inverse Square Law	-2	>0	>0	-2γ	$\frac{\beta}{4\gamma^2}$	$\left(\frac{4}{3}\sqrt{3}-2\right)\gamma$	$(2\sqrt{2}-2)\gamma$	2γ	—	2.4142	$-\frac{\beta}{4\gamma^3}$
-1.0	Rectangular Hyperbola	-1	>0	>0	$-\gamma$	$\frac{\beta}{\gamma}$	$\gamma/3$	γ	3γ	—	3.0	$-\frac{\beta}{\gamma^2}$
-1.5		$-2/3$	>0	>0	$-\frac{2\gamma}{3}$	$\frac{\beta}{\sqrt[3]{4\gamma^2/9}}$	$\frac{2}{3}\left(\frac{8\sqrt{3}}{3}-3\right)\gamma$	$\frac{2}{3}(2\sqrt{2}-1)\gamma$	$\frac{14}{3}\gamma$	—	3.8284	$-\frac{\beta}{\gamma\sqrt[3]{4\gamma^2/9}}$
-2.0	Inverse Square Root Law	$-1/2$	>0	>0	$-\frac{\gamma}{2}$	$\frac{\beta}{\sqrt{\gamma/2}}$	$7\gamma/18$	$3\gamma/2$	$15\gamma/2$	—	5.0	$-\frac{\beta}{\gamma\sqrt{\gamma/2}}$

[a] The curves all have the following characteristics in common:
(1) Finite, positive initial value of $\eta(\xi = 0)$
(2) $d\eta/d\xi < 0$ for all values of ξ
(3) $d^2\eta/d\xi^2 \geq 0$ for all values of ξ
(4) min $\eta = \alpha$ except for the straight line values for which we will ignore beyond the point $(\xi = \gamma, \eta = \alpha)$.

[b] $\xi_p = \gamma\,\delta(1 - q^{1/\delta}), \quad p + q = 1.$

[c] $\xi_{100} = \delta\gamma, \quad \delta > 0.$

[d] $\lambda = \dfrac{(2^{1/\delta})^2 - 1}{(2^{1/\delta})^2 - 2^{1/\delta}}, \quad \delta = -\dfrac{\log 2}{\log(\lambda - 1)}$; for $-\infty < \dfrac{1}{\delta} < +\infty, \quad \lambda > 1.$

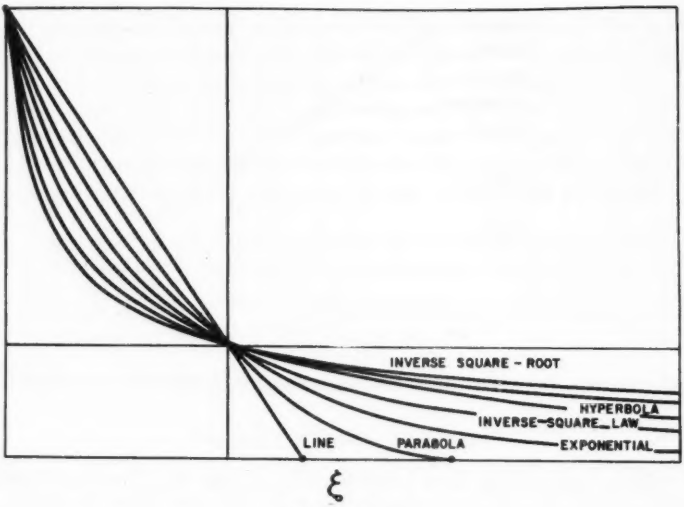


FIGURE 1
SPECIAL EXTINCTION CURVES

special cases enumerated above are summarized in Table 1. In this table the minimum level is taken in all cases to be α and the initial level is measured from this minimum value.

Table 1 includes the *three quarters life* and the *half-life*. The ratio of the two provides a convenient means of estimating δ graphically. From equation (14) we determine the initial value of η to be $\eta_0 = \alpha + \beta(-\gamma\delta)^\delta$ and the minimum value of η to be $\eta_{\min} = \alpha$. The value of ξ corresponding to $(\eta_0 - \alpha)/2$ is the *half-life* and is given by $\xi_{50} = \gamma\delta(1 - 2^{-1/\delta})$. Similarly we obtain the *three-quarters life* $\xi_{75} = \gamma\delta(1 - 4^{-1/\delta})$. The ratio is then $\lambda = \xi_{75}/\xi_{50} = (1 - 4^{-1/\delta})/(1 - 2^{-1/\delta})$, or, inverting, we have

$$\delta^{-1} = -\log_2(\lambda - 1). \tag{16}$$

The parameter λ is given for each of the special cases in Table 1. and the relationship (16) is charted for all cases in Figure 2.

A more general criterion based upon any two percentile-lives is readily found to be

$$\lambda(p_1, p_2) = \xi_{p_1}/\xi_{p_2} = (1 - q_1^{1/\delta})/(1 - q_2^{1/\delta}), \tag{17}$$

where $p_1 + q_1 = p_2 + q_2 = 1$.

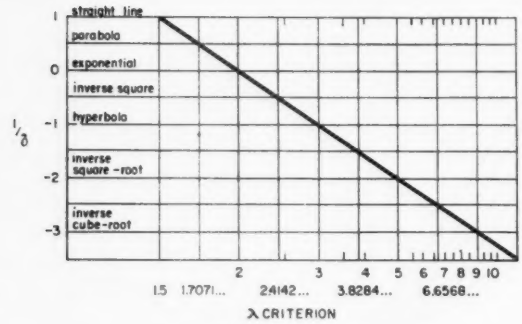


FIGURE 2

RELATIONSHIP BETWEEN THE λ CRITERON AND THE EXPONENTIAL PARAMETER δ

4. THE GAUSSIAN ITERANT

Gauss appears to have been the first to use the Newton-Raphson technique for purposes of finding least squares estimates of non-linear parameters. See Whitaker and Robinson [1944]. In the case of regression with normally distributed errors, Gauss' technique is equivalent to the important *method of scoring* due to Fisher. See Fisher's recent discussion [1956] of the subject.

The technique may be conveniently described in terms of the total derivative. Let us suppose that we have the general regression model

$$y = f(\beta, x) + \epsilon$$

where β is a vector of unknown parameters. The fitted "prediction" equation is, in terms of estimates $\mathbf{b}$,

$$\hat{y} = f(\mathbf{b}, x). \tag{18}$$

By the rule for the total derivative we get $d\hat{y} = \hat{y}_1\, db_1 + \hat{y}_2\, db_2 + \cdots$, where $\hat{y}_i = \partial\hat{y}/\partial b_i$. Then to a first approximation

$$\Delta\hat{y} \doteq \hat{y}_{10}\, \Delta b_1 + \hat{y}_{20}\, \Delta b_2 + \cdots,$$

where $\Delta\hat{y} = y - y_0$, $\Delta b_1 = b_1 - b_{10}$, $\Delta b_2 = b_2 - b_{20}$, $\cdots$. The zero subscript indicates that trial values for the undetermined estimates have been inserted. Thus, we get $\hat{y} \doteq \hat{y}_0 + \Delta b_1\hat{y}_{10} + \Delta b_2\hat{y}_{20} + \cdots$, and finally

$$y \doteq \hat{y}_0 + \Delta b_1\hat{y}_{10} + \Delta b_2\hat{y}_{20} + \cdots + e. \tag{19}$$

The symbol e represents the estimate of the error ϵ. Now (19) is an ordinary multiple linear regression equation and estimates may be

found as before. From the linear regression estimates may be found improved values for the original non-linear regression estimates. Thus, the process is iterated finding successive improvements. It may be seen from (19) that trial values for estimates which are linear in (18) are not needed to prime the iterative process. This point was noted by Stevens [1951] and will be illustrated in the next section. Refer to Deming [1943] for a fuller discussion of this technique of estimation.

5. MAXIMUM LIKELIHOOD ESTIMATION AND ASYMPTOTIC CONFIDENCE LIMITS FOR THE SINGLE PROCESS LAW

Applying the method of the previous section to the single process law we obtain the linearized regression equation:

$$y \doteq a + b(x - m_0)^{d_0} - b\,d_0(x - m_0)^{d_0-1}(m - m_0) + b(x - m_0)^{d_0} \ln (x - m_0)(d - d_0) + e, \tag{20}$$

where a_0 , b_0 , m_0 , and d_0 are trial values and $m = cd$. Note that (20) is linear in a and b and the corrections $(m - m_0)$ and $(d - d_0)$. Thus provisional estimates of a and b and improved estimates of m and d can be found by fitting (20) by least squares. Iteration provides the maximum likelihood estimates. We notice that trial values of the linear coefficients a and b have been eliminated and are thus not required.

For convenience we write

$$\begin{aligned} B_0 &= a, & Z_0 &= 1, \\ B_1 &= b, & Z_1 &= (x - m_0)^{d_0}, \\ B_2 &= -b\,d_0(m - m_0), & Z_2 &= (x - m_0)^{d_0-1}, \\ B_3 &= b(d - d_0), & Z_3 &= (x - m_0)^{d_0} \ln (x - m_0). \end{aligned} \tag{21}$$

Then (20) may be written

$$y \doteq B_0 + B_1Z_1 + B_2Z_2 + B_3Z_3 + e.$$

We have then to find estimates of B_0 , B_1 , B_2 , and B_3 . These are found by multiple regression methods as follows. Let

$$\mathbf{Z} = \begin{bmatrix} 1 & Z_{11} & Z_{12} & Z_{13} \\ 1 & Z_{21} & Z_{22} & Z_{23} \\ \cdots & \cdots & \cdots & \cdots \\ 1 & Z_{n1} & Z_{n2} & Z_{n3} \end{bmatrix}, \quad \mathbf{B} = \begin{bmatrix} B_0 \\ B_1 \\ B_2 \\ B_3 \end{bmatrix}, \quad \mathbf{Y} = \begin{bmatrix} y_1 \\ y_2 \\ \cdots \\ y_n \end{bmatrix}.$$

The normal equations are $\mathbf{Z'ZB} = \mathbf{Z'Y}$ and, if $\mathbf{Z'Z}$ is non-singular, the vector of improved estimates is given by

$$\hat{\mathbf{B}} = (\mathbf{Z'Z})^{-1}\mathbf{Z'Y}. \tag{22}$$

Whenever the error depends upon x in a known way, (22) must be replaced by $\hat{\mathbf{B}} = (\mathbf{Z'WZ})^{-1}\mathbf{Z'WY}$ where $\mathbf{W}$ is a diagonal matrix of weights as in Section 2. From the results of (22) we obtain improved values of m and d by using the relations (21). Thus

$$\begin{aligned} m &= m_0 - \hat{B}_2/d_0\hat{B}_1 , \\ d &= d_0 + \hat{B}_3/\hat{B}_1 . \end{aligned} \tag{23}$$

These improved values replace m_0 and d_0 in (21) and the solution (22) is found again, giving still better values. The process is iterated until constant values of m and d are found to the desired degree of precision. After stable values are obtained we have

$$a = B_0 , \qquad b = B_1 , . \qquad c = m/d, \tag{24}$$

and the estimated curve is given by

$$\hat{y} = a + b(x - m)^d. \tag{25}$$

If $\mu = \gamma\delta$ is known a priori, then the third row and column of $\mathbf{Z'Z}$, the third element of $\mathbf{B}$ and the third element of $\mathbf{Z'Y}$ are deleted. Otherwise, the iterative process is the same as before. Application of this case to a biomathematical model of running records has been made by Turner [1959]. Similarly, when δ is known a priori, the fourth row and column of $\mathbf{Z'Z}$ and the third elements of $\mathbf{B}$ and $\mathbf{Z'Y}$ are deleted. If, as is often the case in extinction curves, the minimum value α is known a priori then y is replaced by $y' = y - \alpha$ and the first row and column of $\mathbf{Z'Z}$ and the first elements of $\mathbf{B}$ and $\mathbf{Z'Y}$ are deleted. Thus, we see that one estimation procedure suffices for the general problem and several special cases as well. However, in the case that δ is a known integer, we may prefer to use the methods of Section 2. If δ is known to be infinite, the methods of Stevens and Pimentel-Gomes referred to earlier should be used.

By examination of the definition of the Z's, equations (21), we see that $\mathbf{Z'Z}$ is singular if $\delta = 0$, 1, or $\pm\infty$. Therefore, the method of this section may be expected to break down in the neighborhood of these points. Trial and error minimization of the residual sum of squares, $S = \sum [y - a - b(x - m)^d]^2$, may then be resorted to, perhaps utilizing some interpolation method such as that proposed by Will [1936]. Values of m and d may be selected and S minimized by ordinary straight

line regression techniques. Thus for the selected values m_1 and d_1 we may regress y on $X = (x - m_1)^{d_1}$, obtaining the minimum S for these values: $S_{11} = \sum (y - \bar{y})^2 - \{[\sum X(y - \bar{y})]^2 / \sum (X - \bar{X})^2\}$. Similarly, values S_{12} for m_1 and d_2, S_{22} for m_2 and d_2, et cetera, may be found and the minimum located.

Alternatively, we may choose selected values of δ only (or of μ only) and use the deleted normal equations to minimize with respect to α, β, and μ (or α, β, and δ). Then simple one-dimensional interpolation will locate the minimum value of S.

When $\mathbf{Z}'\mathbf{Z}$ is only moderately ill-conditioned, we may improve convergence by damping oscillations. Wegstein [1958] recommends using in the $i + 1$-th iteration (in place of m_i and d_i) the modified values

$$\begin{aligned} m_i^* &= u m_{i-1} + v m_i \,, \\ d_i^* &= u\, d_{i-1} + v\, d_i \,. \end{aligned} \tag{26}$$

The following data taken from a sampling experiment [Turner, 1959] will illustrate the iterative process.

x	y
1	162.47
2	108.10
3	81.12
4	66.11
5	55.06
6	49.37
7	39.72
8	33.81
9	30.90
10	30.73

Trial values $m_0 = -1.00$ and $d_0 = -1.00$ were tried and the results below were obtained for successive iterations.

Iteration	m	d
0	−1.00	−1.00
1	− .23	− .56
2	− .38	− .69
3	− .43	− .67
4	− .44	− .67

Asymptotic confidence limits are easily found. After the final iteration the asymptotically unbiassed estimate of σ^2 is given by

$$s^2 = (\sum y^2 - B_0 \sum y - B_1 \sum Z_1 y - B_2 \sum Z_2 y - B_3 \sum Z_3 y)/(n - 4). \quad (27)$$

Let us denote by c_{ij} the element in the ith row and jth column of $(\mathbf{Z}'\mathbf{Z})^{-1}$. It has been well known since Gauss that the variance σ_f^2 of any function of the B's (f say) is asymptotically given by

$$\sigma_f^2 = \sigma^2 \sum_{i=0}^{3} \sum_{j=0}^{3} c_{ij} f_i f_j ,$$

where $f_i = \partial f/\partial B_i$ and $f_j = \partial f/\partial B_j$. We may use as the estimated variance of the function the quantity

$$s_f^2 = s^2 \sum_{i=0}^{3} \sum_{j=0}^{3} c_{ij} f_i f_j . \quad (28)$$

Then from (23) and (24) using (28) we find the estimated asymptotic variances for a, b, m, d, and c to be

$$\begin{aligned} s_a^2 &= c_{00} s^2, \qquad s_m^2 = c_{22} s^2/b^2 d^2, \\ s_b^2 &= c_{11} s^2, \qquad s_d^2 = c_{33} s^2/b^2, \\ s_c^2 &= [(c_{22}/b^2 d^2 m^2) - (2c_{23}/b^2 d^2) + (m^2 c_{33}/b^2 d^4)] s^2. \end{aligned} \quad (29)$$

Finally, for y, using (25) and (28), we find the asymptotic variance

$$s_{\hat{y}}^2 = s^2 \sum_{i=0}^{3} \sum_{j=0}^{3} c_{ij} Z_i Z_j . \quad (30)$$

From (29) and (30) we can construct asymptotic confidence limits. We get

$$\begin{aligned} a - t_\pi s_a \le \alpha \le a + t_\pi s_a , \\ b - t_\pi s_b \le \beta \le b + t_\pi s_b , \\ m - t_\pi s_m \le \mu \le m + t_\pi s_m , \\ d - t_\pi s_d \le \delta \le d + t_\pi s_d , \\ c - t_\pi s_c \le \gamma \le c + t_\pi s_c , \\ \hat{y} - t_\pi s_{\hat{y}} \le E(y) \le \hat{y} + t_\pi s_{\hat{y}} , \end{aligned} \quad (31)$$

with $(1 - \pi)$ confidence each where t_π is Student's t for the π level of significance with $n - 4$ degrees of freedom. The last confidence statement provides confidence limits for the true value of $\eta = E(y)$

for a given x. See Deming [1943] for detailed discussion of these methods for any model. It must be emphasized that (31) provides individual confidence statements at the assigned $(1 - \pi)$ level of confidence. Of course, the joint confidence level is much less than $(1 - \pi)$.

These confidence statements provide a ready guide to the tenability of various hypotheses about the unknown parameters in the single process law. If it is specifically hypothesized on theoretical grounds that some particular parameter takes a given value (e.g., $H_0 : \delta = \delta_0$), then we may test the concordance of the data with this hypothesis by seeing whether or not the hypothesized value lies within the confidence interval. If the hypothesized value is in fact tenable, we may wish to refit the regression equation after making the proper deletions for a known a priori parameter. On the other hand, if there is no theoretical reason for making such a hypothesis, it does not seem wise to recompute the curve for some convenient value of the parameter lying within the confidence interval. Such practice will lead to a false sense of confidence in that narrower confidence limits will result from fixing the parameter.

6. PARABOLIC CONFIDENCE LIMITS FOR SMALL SAMPLES

The asymptotic confidence limits described in the foregoing section may be expected to give adequate results for large samples or even for quite modest samples if the error rate is small. For example, in a recent sampling investigation [Turner, 1959], it was found that, with a sample size of ten equally spaced points covering the major portion of the curve and with a coefficient of variation of two percent at the center of the curve, the sampling variation of d, the estimate of δ, was quite accurately described by the asymptotic distribution. However, when the error rate is much larger, it may be supposed that the asymptotic distribution will not suffice for construction of tests or confidence limits.

We will now describe a method of constructing an exact test and corresponding confidence limits based upon a class of "parabolic" alternative hypotheses.

We consider the null hypothesis

$$H_0 : \mu - \mu_0 = \delta - \delta_0 = 0. \tag{32}$$

Thus, when the null hypothesis H_0 is true, we have the model

$$y_i = \alpha + \beta(x_i - \mu_0)^{\delta_0} + \epsilon_i , \tag{33}$$

where $i = 1, 2, \cdots, n$ for sample size n.

Let $Z_{i0} = (x_i - \mu_0)^{\frac{1}{2}}$; then the model (33) for H_0 true is written

$$y_i = \alpha + \beta Z_{i0} + \epsilon_i ,$$

the model for a straight line.

Now, if H_0 is not true, we could write

$$y_i = f(Z_{i0}) + \epsilon_i . \tag{34}$$

Expanding (34) in a Maclaurin series and preserving terms through the quadratic, we get

$$y_i \doteq B_0 + B_1 Z_{i0} + B_2 Z_{i0}^2 + \epsilon_i .$$

If we suppose that coefficients of terms beyond the quadratic are negligible, then the null hypothesis,

$$H_0' : B_2 = 0,$$

is equivalent to (32). An exact test of H_0' is well known and is easily performed.

Let

$$\begin{aligned}
S_{11} &= \sum Z_{i0}^2 - [(\sum Z_{i0})^2/n], \\
S_{12} &= \sum Z_{i0}^3 - [(\sum Z_{i0})(\sum Z_{i0}^2)/n], \\
S_{1y} &= \sum Z_{i0} y_i - [(\sum Z_{i0})(\sum y_i)/n], \\
S_{22} &= \sum Z_{i0}^4 - [(\sum Z_{i0}^2)^2/n], \\
S_{2y} &= \sum Z_{i0}^2 y_i - [(\sum Z_{i0}^2)(\sum y_i)/n], \\
S_{yy} &= \sum y_i^2 - [(\sum y_i)^2/n],
\end{aligned} \tag{35}$$

where all summations are over $i = 1, 2, \cdots, n$. Then we have estimates

$$\begin{aligned}
\hat{B}_1 &= (S_{22}S_{1y} - S_{12}S_{2y})/(S_{11}S_{22} - S_{12}^2), \\
\hat{B}_2 &= (S_{11}S_{2y} - S_{12}S_{1y})/(S_{11}S_{22} - S_{12}^2).
\end{aligned} \tag{36}$$

Then the residual sum of squares about the fitted quadratic curve is given by

$$SSE = S_{yy} - \hat{B}_1 S_{1y} - \hat{B}_2 S_{2y} . \tag{37}$$

Similarly, the residual sum of squares about the straight line is given by

$$SSE' = S_{yy} - (S_{1y}^2/S_{11}). \tag{38}$$

Then an exact F-test for $H_0' : B_2 = 0$, which is approximately equivalent to $H_0 : \mu - \mu_0 = \delta - \delta_0 = 0$, is performed by calculating

$$F = (n - 3)(SSE' - SSE)/SSE. \tag{39}$$

Then if $F \geq F_\pi$, the tabular value of F with 1 and $n - 3$ degrees of freedom, the null hypothesis is rejected at the π level of significance.

A joint confidence region, with $(1 - \pi)$ confidence, for μ and δ (and hence γ and δ) may be found by determining those values of μ_0 and δ_0 which ensure that $F \leq F_\pi$. This may be done most conveniently, perhaps, by calculating F for various selected values of μ_0 and δ_0 and then interpolating to find the confidence contours. A numerical example when μ is known a priori has been given by Turner [1959].

In some cases it may be necessary to retain higher-power terms in the Maclaurin expansion. Since then a wider class of alternative hypotheses would be admitted, the power of the test against any specific hypothesis would in general be lower.

When observations are replicated for various values of x, the numerator of (39) may be tested against the *within replicate* sum of squares to give a more powerful test. If the *within replicate* sum of squares is denoted SSE^*, we have the test

$$F = n(r - 1)(SSE' - SSE)/SSE^*, \tag{40}$$

with 1 and $n(r - 1)$ degrees of freedom, where n is the number of points on the curve as before and r is the number of replicates. A confidence region may be found corresponding to this test just as before.

A test similar in concept to the parabolic test has been proposed by Williams [1959] and is discussed in connection with the single process law by Turner [1959]. Williams' test is not likely to be as powerful as the parabolic test whenever there is more than a single non-linear parameter, as in the present case. If either μ or δ is known a priori then Williams' test should be considered as an alternative to the parabolic test.

Hotelling [1939] has proposed a method of constructing exact tests which could be applied to the construction of a test of the hypothesis $\beta = 0$ in the single process law. However β is the constant of integration and is generally of little interest since the character of the process is not determined by this constant.

7. NON-LINEAR PATH REGRESSION AND THE SINGLE PROCESS LAW

Let us suppose that we have p "secondary" variables which are causally related to one another and to a set of q "primary" or "controllable" variables. We imagine that the q primary variables (denoted $\xi_a, \xi_b, \cdots, \xi_q$) have values which can be chosen at will by the experimenter. In particular, it is possible that they are randomly chosen but this is generally not so in laboratory experimentation. The p

secondary variables (denoted η_1 , η_2 , $\cdots$, η_p) are then supposed to be completely determined. The rates of change of one variable with respect to another are determined by a matrix of partial derivatives

$$\mathbf{H}' = \left[\begin{array}{cccc} \eta_{1a} & \eta_{2a} & \cdots & \eta_{pa} \\ \eta_{1b} & \eta_{2b} & \cdots & \eta_{pb} \\ \cdots & \cdots & \cdots & \cdots \\ \eta_{1q} & \eta_{2q} & \cdots & \eta_{pq} \\ \hline \eta_{11} & \eta_{21} & \cdots & \eta_{p1} \\ \eta_{12} & \eta_{22} & \cdots & \eta_{p2} \\ \cdots & \cdots & \cdots & \cdots \\ \eta_{1p} & \eta_{2p} & \cdots & \eta_{pp} \end{array}\right] = \begin{bmatrix} \mathbf{H}'_\xi \\ \mathbf{H}'_\eta \end{bmatrix}. \tag{41}$$

When $\eta_{ij} = \alpha_{ij}$, a constant, then the relations between all of the variables are linear. A recent review of linear path regression analysis is that of Turner and Stevens [1959]. See also Turner [1959]. The method of path regression analysis, originally described and named by Wright [1921], has been applied only in the case of linear relations, with one exception [Tukey, 1954]. The method, however, only attains its full power when the relations between variables are described by non-linear equations. This is partly what Tukey meant when in his critique [Tukey, 1954] he said that classical path coefficients are "very good, but they don't go far enough". For example, the important field of chemical reaction kinetics requires a path analysis wherein the relations between variables are governed by the *law of mass action*.

In many cases we may regard η_{ij} to be a function of η_i and ξ_j (or η_j) only. In particular, we may consider that the relations between variables follow the single process law.

Let a matrix of rate coefficients be

$$\mathbf{\Delta}' = \left[\begin{array}{cccc} \delta_{1a} & \delta_{2a} & \cdots & \delta_{pa} \\ \delta_{1b} & \delta_{2b} & \cdots & \delta_{pb} \\ \cdots & \cdots & \cdots & \cdots \\ \delta_{1q} & \delta_{2q} & \cdots & \delta_{pq} \\ \hline 1 & \delta_{21} & \cdots & \delta_{p1} \\ \delta_{12} & 1 & \cdots & \delta_{p2} \\ \cdots & \cdots & \cdots & \cdots \\ \delta_{1p} & \delta_{2p} & \cdots & 1 \end{array}\right] = \begin{bmatrix} \mathbf{\Delta}'_\xi \\ \mathbf{\Delta}'_\eta \end{bmatrix}$$

and diagonal matrices be

$$\mathbf{D}_\xi = \begin{bmatrix} \xi_a & 0 & \cdots & 0 \\ 0 & \xi_b & \cdots & \cdots \\ \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & \xi_q \end{bmatrix}, \qquad \mathbf{D}_\mu = \begin{bmatrix} \mu_a & 0 & \cdots & 0 \\ 0 & \mu_b & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & \mu_q \end{bmatrix},$$

$$\mathbf{D}_\eta = \begin{bmatrix} \eta_1 & 0 & \cdots & 0 \\ 0 & \eta_2 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & \eta_p \end{bmatrix}, \qquad \mathbf{D}_\alpha = \begin{bmatrix} \alpha_1 & 0 & \cdots & 0 \\ 0 & \alpha_2 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & \cdots & \alpha_p \end{bmatrix}.$$

Now we will consider the multivariate analogue of the single process law given by

$$\mathbf{H}' = \begin{bmatrix} \mathbf{H}'_\xi \\ \mathbf{H}'_\eta \end{bmatrix} = \begin{bmatrix} (\mathbf{D}_\xi - \mathbf{D}_\mu)^{-1} \, \mathbf{\Delta}'_\xi (\mathbf{D}_\eta - \mathbf{D}_\alpha) \\ (\mathbf{D}_\eta - \mathbf{D}_\alpha)^{-1} \, \mathbf{\Delta}'_\eta (\mathbf{D}_\eta - \mathbf{D}_\alpha) \end{bmatrix}. \tag{42}$$

The analogy in form to the univariate differential equation (13) is evident. A solution of (42) is

$$\begin{aligned}
\eta_1 &= \alpha_1 + \beta_1 (\xi_a - \mu_a)^{\delta_{1a}} (\xi_b - \mu_b)^{\delta_{1b}} \cdots \\
&\qquad \cdot (\xi_q - \mu_q)^{\delta_{1q}} (1) (\eta_2 - \alpha_2)^{\delta_{12}} \cdots (\eta_p - \alpha_p)^{\delta_{1p}} \\
\eta_2 &= \alpha_2 + \beta_2 (\xi_a - \mu_a)^{\delta_{2a}} (\xi_b - \mu_b)^{\delta_{2b}} \cdots \\
&\qquad \cdot (\xi_q - \mu_q)^{\delta_{2q}} (\eta_1 - \alpha_1)^{\delta_{21}} (1) \cdots (\eta_p - \alpha_p)^{\delta_{2p}} \\
&\cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \\
\eta_p &= \alpha_p + \beta_p (\xi_a - \mu_a)^{\delta_{pa}} (\xi_b - \mu_b)^{\delta_{pb}} \cdots \\
&\qquad \cdot (\xi_q - \mu_q)^{\delta_{pq}} (\eta_1 - \alpha_1)^{\delta_{p1}} (\eta_2 - \alpha_2)^{\delta_{p2}} \cdots (1).
\end{aligned} \tag{43}$$

Thus (43) are the "structural equations" for the causal network arising from allowing each pathway to individually follow the single process law.

As with linear path regression analysis many of the pathways may be non-existent for any particular problem. These restrictions on the structural equations are made simply by setting the corresponding δ to zero.

Note that the structural equations (43) relate "true" variables and parameters. No stochastic variables have been considered yet, and thus, we may transform the equations arbitrarily. We take logs as follows:

$$\begin{aligned}
\eta_1^* &= \log (\eta_1 - \alpha_1), & \xi_a^* &= \log (\xi_a - \mu_a), & \alpha_1^* &= \log \beta_1 , \\
\eta_2^* &= \log (\eta_2 - \alpha_2), & \xi_b^* &= \log (\xi_b - \mu_b), & \alpha_2^* &= \log \beta_2 , \\
\cdots & \quad \cdots & \cdots & \quad \cdots & \cdots & \quad \cdots \\
\eta_p^* &= \log (\eta_p - \alpha_p), & \xi_q^* &= \log (\xi_q - \mu_q), & \alpha_p^* &= \log \beta_p ,
\end{aligned}$$

and $\alpha_{ij}^* = \delta_{ij}$. Then (43) becomes

$$\begin{aligned}
\eta_1^* &= \alpha_1^* + \alpha_{1a}^*\xi_a^* + \alpha_{1b}^*\xi_b^* + \cdots + \alpha_{1c}^*\xi_c^* + \alpha_{12}^*\eta_2^* + \cdots + \alpha_{1p}^*\eta_p^* \\
\eta_2^* &= \alpha_2^* + \alpha_{2a}^*\xi_a^* + \alpha_{2b}^*\xi_b^* + \cdots + \alpha_{2c}^*\xi_c^* + \alpha_{21}^*\eta_1^* + \cdots + \alpha_{2p}^*\eta_p^* \\
&\cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \quad \cdots \\
\eta_p^* &= \alpha_p^* + \alpha_{pa}^*\xi_a^* + \alpha_{pb}^*\xi_b^* + \cdots + \alpha_{pc}^*\xi_c^* + \alpha_{p1}^*\eta_1^* + \alpha_{p2}^*\eta_2^* + \cdots
\end{aligned} \tag{44}$$

These transformed structural equations are identical in form with those underlying linear path regression analysis. For a more detailed comparison see Turner [1959]. We may write (44) in matrix notation as follows:

$$(\mathbf{A}_1 , \mathbf{A}_2)\begin{bmatrix}\xi \\ \mathbf{n}\end{bmatrix} = \mathbf{n} \tag{45}$$

where

$$(\mathbf{A}_1 , \mathbf{A}_2) = \left[\begin{array}{cccc|cccc} \alpha_1^* & \alpha_{1a}^* & \cdots & \alpha_{1c}^* & 0 & \alpha_{12}^* & \cdots & \alpha_{1p}^* \\ \alpha_2^* & \alpha_{2a}^* & \cdots & \alpha_{2c}^* & \alpha_{21}^* & 0 & \cdots & \alpha_{2p}^* \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \alpha_p^* & \alpha_{pa}^* & \cdots & \alpha_{pc}^* & \alpha_{p1}^* & \alpha_{p2}^* & \cdots & 0 \end{array}\right],$$

and

$$\xi' = (1\ \xi_a^* \cdots \xi_c^*),$$

$$\mathbf{n}' = (\eta_1^*\ \eta_2^* \cdots \eta_p^*).$$

From (45) we get by multiplication

$$\mathbf{A}_1\xi + \mathbf{A}_2\mathbf{n} = \mathbf{n} \tag{46}$$

and

$$\mathbf{n} - \mathbf{A}_2\mathbf{n} = \mathbf{A}_1\xi$$

$$(\mathbf{I} - \mathbf{A}_2)\mathbf{n} = \mathbf{A}_1\xi.$$

If $(\mathbf{I} - \mathbf{A}_2)$ is non-singular, we get the reduced transformed structural equations.

$$\mathbf{n} = (\mathbf{I} - \mathbf{A}_2)^{-1}\mathbf{A}_1\xi. \tag{47}$$

Thus, the transformed secondary variables $\mathbf{n}$ are expressed as linear functions of the transformed primary variables ξ and it is seen that the necessary and sufficient condition for this to be possible is that $(\mathbf{I} - \mathbf{A}_2)$ be non-singular.

Inverse log transformation will then provide reduced structural equations in terms of the original variables also such that each secondary variable is a function of just the primary variables.

There are several types of causal relationships which are conveniently distinquished. First of all there is the situation in which a single secondary variable is determined by one or more primary variables. This is the case of "ordinary regression", the single structural equation being the non-linear analogue of that corresponding to the usual multiple regression model. A second case is the situation in which two or more secondary variables are jointly determined by some or all of a common set of primary variables. We term this case the case of "joint" regression. In a third situation there is a chain of cause and effect leading from one or more primary variables to a secondary variable and then on to still another "secondary" variable. This case we term the case of "chain" regression. A final type involves cycles of causation or "feedback" from one secondary variable to another and back again after possibly passing through one or more other secondary variables. This is the case of "cyclic" regression. All of these cases individually or in combination have been synoptically treated in what has gone before. Here we wish only to note that the several cases are distinguished by having different kinds of $(\mathbf{I} - \mathbf{A}_2)$ matrices. For this reason we term $(\mathbf{I} - \mathbf{A}_2)$ the "classification" matrix. It may be verified that regression type and $(\mathbf{I} - \mathbf{A}_2)$ are related as follows:

regression type	$(\mathbf{I} - \mathbf{A}_2)$
Ordinary	1 (scalar)
Joint	I
Chain	Triangular
Cyclic (feedback)	Non-triangular

The heavy algebra implied by (47) may be conveniently by-passed by the use of algorithms (see Turner and Stevens, [1959]) when the classification matrix $(\mathbf{I} - \mathbf{A}_2)$ is triangular, that is, when there is no feedback in the system. General algorithms are also available.

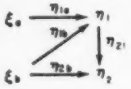
We now consider three elementary systems to illustrate the foregoing and to provide concreteness.

Consider first, the "multiple regression" analogue, with the path diagram below.

The structural equation is then found to be

$$\eta_1 = \alpha_1 + \beta_1(\xi_a - \mu_a)^{\delta_{1a}}(\xi_b - \mu_b)^{\delta_{1b}}. \tag{48}$$

A second example involves ordinary, joint, and chain regression.



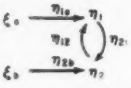
The structural equations are

$$\begin{aligned}\eta_1 &= \alpha_1 + \beta_1(\xi_a - \mu_a)^{\delta_{1a}}(\xi_b - \mu_b)^{\delta_{1b}}, \\ \eta_2 &= \alpha_2 + \beta_2(\xi_b - \mu_b)^{\delta_{2b}}(\eta_1 - \alpha_1)^{\delta_{21}}.\end{aligned} \tag{49}$$

Reduction by use of the algorithms leads to

$$\begin{aligned}\eta_1 &= \alpha_1 + \beta_1(\xi_a - \mu_a)^{\delta_{1a}}(\xi_b - \mu_b)^{\delta_{1b}}, \\ \eta_2 &= \alpha_2 + \beta_2\beta_1^{\delta_{21}}(\xi_a - \mu_a)^{\delta_{21}\delta_{1a}}(\xi_b - \mu_b)^{\delta_{2b}+\delta_{21}\delta_{1b}}\end{aligned} \tag{50}$$

A final example is one involving feedback. The path diagram is as below



We have the structural equations

$$\begin{aligned}\eta_1 &= \alpha_1 + \beta_1(\xi_a - \mu_a)^{\delta_{1a}}(\eta_2 - \alpha_2)^{\delta_{12}}, \\ \eta_2 &= \alpha_2 + \beta_2(\xi_b - \mu_b)^{\delta_{2b}}(\eta_1 - \alpha_1)^{\delta_{21}}.\end{aligned} \tag{51}$$

Reduction by (47) then gives

$$\begin{aligned}\eta_1 &= \alpha_1 + \beta_1^{1/(1-\delta_{12}\delta_{21})}\beta_2^{\delta_{12}(1-\delta_{12}\delta_{21})} \\ &\quad \cdot(\xi_a - \mu_a)^{\delta_{1a}/(1-\delta_{12}\delta_{21})}(\xi_b - \mu_b)^{\delta_{12}\delta_{2b}/(1-\delta_{12}\delta_{21})} \\ \eta_2 &= \alpha_2 + \beta_1^{\delta_{21}/(1-\delta_{12}\delta_{21})}\beta_2^{1/(1-\delta_{12}\delta_{21})} \\ &\quad \cdot(\xi_a - \mu_a)^{\delta_{21}\delta_{1a}/(1-\delta_{12}\delta_{21})}(\xi_b - \mu_b)^{\delta_{2b}/(1-\delta_{12}\delta_{21})}\end{aligned} \tag{52}$$

Let us assume independent additive normal errors in the observable variable y and non-existent errors in the observable variable x so that we have $x_i = \xi_i$ for $i = 1, 2, \cdots, q$, and $y_i = \eta_i + \epsilon_i$ for $i = 1, 2, \cdots, p$. We further assume that the ϵ_i are uncorrelated from one variable to another. Then after reduction we will have p independent non-linear regression equations, each of the form

$$\hat{y} = B_0 + B_1(x_a - M_a)^{D_a}(x_b - M_b)^{D_b} \cdots (x_q - M_q)^{D_q} \tag{53}$$

where $D_a, D_b, \cdots, D_q$ are functions of the $\hat{\delta}$'s and B_1 is a function of the $\hat{\beta}$'s and $\hat{\delta}$'s.

Now precisely the same problem of "identification" which plagues

linear path analysis arises again here. The problem of estimation is much simplified if we can confine our attention to finding the B's and D's. In certain cases it is then possible to solve for estimates of the original parameters in terms of just the B's and D's. When this is possible, we say the system is *just-identified.* See Turner and Stevens [1959] for discussion. In the present instance we will restrict consideration to the just-identified case.

Again we make use of the Gaussian iterant. We first obtain trial estimates $M_{a0}, M_{b0}, \cdots, M_{q0}, D_{a0}, D_{b0}, \cdots, D_{q0}$. Then we compute:

$$\begin{aligned}
Z_{10} &= (x_a - M_{a0})^{D_{a0}}(x_b - M_{b0})^{D_{b0}} \cdots (x_q - M_{q0})^{D_{q0}},\\
Z_{20} &= Z_{10}/(x_a - M_{a0}),\\
Z_{30} &= Z_{10}/(x_b - M_{b0}),\\
&\cdots \quad \cdots \quad \cdots\\
Z_{q+1,0} &= Z_{10}/(x_q - M_{q0}),\\
Z_{q+2,0} &= Z_{10} \log_e (x_a - M_{a0}),\\
Z_{q+3,0} &= Z_{10} \log_e (x_b - M_{b0}),\\
&\cdots \quad \cdots \quad \cdots\\
Z_{2q+1,0} &= Z_{10} \log_e (x_q - M_{q0}),
\end{aligned} \tag{54}$$

for all observational vectors. In addition we define:

$$\begin{aligned}
B_2 &= -B_{10}\, D_{a0}(M_a - M_{a0}), & B_{q+2} &= B_{10}(D_a - D_{a0}),\\
B_3 &= -B_{10}\, D_{b0}(M_b - M_{b0}), & B_{q+3} &= B_{10}(D_b - D_{b0}),\\
&\cdots \quad \cdots \quad \cdots & &\cdots \quad \cdots \quad \cdots\\
B_{q+1} &= -B_{10}\, D_{q0}(M_q - M_{q0}), & B_{2q+1} &= B_{10}(D_q - D_{q0}).
\end{aligned} \tag{55}$$

Using the device of the total derivative we obtain the approximate linearization

$$\hat{y} \doteq B_0 + B_1 Z_{10} + B_2 Z_{20} + \cdots + B_{2q+1} Z_{2q+1} \tag{56}$$

with which to replace (53). By the usual methods of linear regression we now obtain the estimates $B_0, B_1, \cdots, B_{2q+1}$ and from (55) we get the improved estimates $M_a, \cdots, D_q$. These now can be used to replace $M_{a0}, \cdots, D_{q0}$ in (54) and the entire process reiterated until stable estimates are obtained.

If any subset of parameters is known a priori then, as in the simple regression case of Section 3, the appropriate Z's are simply omitted

and the analysis carried out without them. For example, if it is known that all processes have vertical asymptotes zero, then we omit Z_{20} through $Z_{q+1,0}$.

When there is more than a single response variable, the application of (56) separately to each provides multiple estimates for the vertical asymptotes M_a, M_b, $\cdots$, M_q. In order to provide unique, efficient estimates of these values, we fit, instead of (56), the family of hyperplanes

$$\hat{y}_i \doteq B_{0i} + B_{1i}Z_{10i} + B_2Z_{20i} + \cdots + B_{q+1}Z_{q+1,0i} + B_{q+2,i}Z_{q+2,0i} + \cdots + B_{2q+1,i}Z_{2q+1,0i} \qquad (57)$$

where $i = 1, 2, \cdots, p$ and B_2, B_3, $\cdots$, B_{q+1} are common for all i. Linear regression theory again provides the minimum variance unbiassed estimators for fitting (57).

Now the final estimates of the B's, M's and D's will not be minimum variance unbiassed estimates but they will be maximum likelihood estimates and hence they will be consistent, efficient and invariant under transformation. Thus, since we have assumed a condition of "just-identification" we can solve for estimates of the δ's and these estimates will also be maximum likelihood estimates.

If we were to have an under-identified system, then the methods of this section would be as satisfactory as any. However, if we were to have an over-identified system, another procedure would be required. Perhaps it would be best in that case to simply determine the maximum likelihood estimators directly from the special case being considered. A general computing method appears to be too cumbersome for all possibilities of over-identification.

Asymptotic tests and confidence limits for the just-identified case are found as before by applying linear results to the final iteration. The parabolic test is also applicable to the general case of this section, but, of course, the numerical difficulties are much increased. These may not be prohibitive in the simplest cases, however.

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ON THE ANALYSIS OF SPLIT-PLOT EXPERIMENTS

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Summary.

A crucial question in the analysis of split-plot experiments is whether or not the interaction between subplot treatments and replications should be pooled with the three-factor interaction of main-plot treatments, subplot treatments, and replications, the result being called subplot error. A brief history of the disagreement over this question is given, along with a rule for deciding, on the basis of a preliminary test of significance, whether or not to pool. Several numerical examples are cited, and one of these is worked out in detail.

1. *History.*

The simplest type of split-plot experiment is one in which a levels of one treatment (the main plot treatment A) are arranged in a randomized blocks design with r blocks (replications R), and b levels of a second treatment (the subplot treatment B) are assigned at random, one to each of b subplots in each of the ar whole plots. It is assumed that a correlation ρ exists between the experimental errors for any two subplots in the same whole plot, but that experimental errors for subplots in different whole plots are uncorrelated. Historically, most statisticians have assumed that interactions between treatments and replications do not really exist. Hence they have computed a sum of squares for subplot error without showing a breakdown into sums of squares for $B \times R$ and $A \times B \times R$, and have used the mean square for subplot error for testing the significance of both B and $A \times B$. Some (see, for example, Federer [5, p. 274]) have even asserted that $B \times R$ and $A \times B \times R$ are confounded with each other and hence are really not separable, though it is possible to compute the two interactions arithmetically. On the other hand, Anderson and Bancroft [1, p. 350] have opined that if the subplot treatments are considered to be random, it is necessary to separate $B \times R$ and $A \times B \times R$. Among those who have considered the case in which the interactions between treatments and replications are not assumed to be zero are Wilk and Kempthorne

[10, pp. 101–102]. Chew [3, pp. 45–49] has assumed only that the three-factor interaction is zero. In either of these cases, $B \times R$ and $A \times B \times R$ must be separated, since the expected values of their mean squares are not identical. We shall consider cases in which it is not known a priori whether or not the interactions between treatments and replications are zero. We shall assume that R (replications) is always a random factor, and consider four cases: (1) A and B both random; (2) A fixed and B random; (3) A random and B fixed; and (4) A and B both fixed. Of these, (4) seems to occur most often in practice. We shall define the variance of an effect involving a fixed factor having f levels with $(f - 1)$ instead of f in the denominator. The expected mean squares are summarized in Table 1, along with the test ratios for A, B, and $A \times B$.

TABLE 1

SUMMARY OF EXPECTED VALUES OF MEAN SQUARES AND TEST RATIOS FOR SPLIT-PLOT EXPERIMENTS

Source	Mean Square	Expected Value of Mean Square (all factors random)* σ_e^2	σ_r^2	σ_{er}^2	σ_b^2	σ_{eb}^2	σ_{br}^2	σ_{ebr}^2	σ^2
Main-plot									
Treatments A	S_a	br		b		$[r]$		[1]	$1 + \overline{b-1}\rho$
Replications R	S_r		ab	(b)			$[a]$	[(1)]	$1 + \overline{b-1}\rho$
$A \times R$	S_{er}			b				[1]	$1 + \overline{b-1}\rho$
Subplot									
treatments B	S_b				ar	(r)	a	(1)	$1 - \rho$
$A \times B$	S_{eb}					r		1	$1 - \rho$
$B \times R$	S_{br}						a	(1)	$1 - \rho$
$A \times B \times R$	S_{ebr}							1	$1 - \rho$

*For brevity, we show multipliers of components of variance in the table; thus, for example, $E(S_{ebr}) = \sigma^2_{ebr} + (1 - \rho)\sigma^2$. If A is fixed, omit components whose coefficients are enclosed in parentheses. If B is fixed, omit components whose coefficients are enclosed in brackets. (It is assumed that R is always a random factor.)

Test Ratios for A

If B is fixed, use S_e/S_{er} (exact test). If B is random, use S_e/S_{er} (assumes $\sigma_{eb}^2 = 0$) or S_e/S_{eb} (assumes $\sigma^2_{er} = 0$, $\rho = 0$). Satterthwaite test: $S_e/(S_{er} + S_{eb} - S_{ebr})$; Cochran test: $(S_e + S_{ebr})/(S_{er} + S_{eb})$.

Test Ratios for B

If A is fixed, use S_b/S_{br} (exact test). If A is random, use S_b/S_{br} (assumes $\sigma_{eb}^2 = 0$) or S_b/S_{eb} (assumes $\sigma^2_{br} = 0$). Satterthwaite test: $S_b/(S_{br} + S_{eb} - S_{ebr})$; Cochran test: $(S_b + S_{ebr})/(S_{br} + S_{eb})$.

Test Ratio for A × B

Use S_{eb}/S_{ebr} (exact test)

(One is usually not interested in testing significance of R and its interactions.)

2. *Decision Rule for Pooling.*

We find in Table 1 that the expected value of the mean square for the $A \times B \times R$ interaction is $\sigma^2_{abr} + (1 - \rho)\sigma^2$. The expected value of the mean square for the $B \times R$ interaction is $a\sigma^2_{br} + \sigma^2_{abr} + (1 - \rho)\sigma^2$ if A is random, but it is $a\sigma^2_{br} + (1 - \rho)\sigma^2$ if A is fixed. In either case, the expected values of the mean squares for $B \times R$ and for $A \times B \times R$ are not identical; hence they should not be pooled unless this action is indicated by the results of a preliminary test of significance. This preliminary test is a test of the null hypothesis $H_0 : E(S_{br}) = E(S_{abr})$. Since R is assumed to be random, both $S_{br}/E(S_{br})$ and $S_{abr}/E(S_{abr})$ have central χ^2/d. f. distributions. Hence under H_0 the test ratio S_{br}/S_{abr} has a central F distribution. The form of this preliminary test depends upon whether A is random or fixed. If A is random, H_0 reduces to $H_0' : \sigma^2_{br} = 0$, the expected value of the mean square for $B \times R$ is greater than or equal to the expected value of the mean square for $A \times B \times R$, and the required preliminary test of significance is a one-sided test on the ratio of the mean square for $B \times R$ to the mean square for $A \times B \times R$. If this ratio does not exceed a certain percentage point of the F distribution, the two mean squares are pooled; otherwise, they are not pooled. This problem has been studied by Bozivich, Bancroft and Hartley [2], who recommend a preliminary test of size α, where $.25 \leq \alpha \leq .50$. On the other hand, if A is fixed, H_0 reduces to $H_0'' : \sigma^2_{abr} = a\sigma^2_{br}$, nothing can be said about the relative magnitude of the expected mean squares for $B \times R$ and $A \times B \times R$, and the procedure recommended by Bozivich, Bancroft and Hartley must be modified slightly; the preliminary test of significance is a two-sided test of size α, with probability $\alpha/2$ in each tail of the F distribution. In this case, it is not possible to make a test of size $\alpha = .25$ without computing a special table, since no table of the upper 12.5 percent points of the F distribution is available. Tests of size $\alpha = .20$ and $\alpha = .50$ are possible, using tables of the upper 10 percent and 25 percent points of the F distribution tabulated by Merrington and Thompson[7].

3. *Examples.*

Five numerical examples have been taken from the literature and the subplot error for each has been subdivided into $B \times R$ and $A \times B \times R$ interactions. In each of these examples, it appears reasonable to assume that both A and B are fixed factors, so that the preliminary test of significance will be two-sided. Table 2 gives, for each example, the source of the data, the mean squares and the numbers of degrees of freedom for $B \times R$ and for $A \times B \times R$, the ratio of the larger mean

TABLE 2

PRELIMINARY TESTS FOR POOLING IN SPLIT-PLOT EXPERIMENTS

Source Code	$B \times R$ Interaction M. S.	d.f.	$A \times B \times R$ Interaction M. S.	d.f.	Ratio = Larger M. S. / Smaller M. S.	Critical Values $F_{.10}$	$F_{.25}$
(1)	0.0367	15	0.0236	30	1.56	1.72	1.32
(2)	15.29	6	25.50	42	1.67	2.78	1.75
(3)	28.08	9	13.18	27	2.13	1.87	1.37
(4)	119.21	15	206.02	30	1.73	1.87	1.40
(5)	19.36	70	21.03	140	1.09	1.32	1.16

Sources: (1) Snedecor [9, Table 11.35, p. 310], (2) Federer [5, Table X--2, p. 276], (3) Anderson and Bancroft [1, Table 23.2, p. 348], (4) Rider [8, Exercise 4, p. 191], taken from Yates [11], (5) Cochran and Cox [4, Table 7.5, p. 225].

square to the smaller and the upper 10 percent and 25 percent points of the F distribution. If we use a preliminary test of size $\alpha = .50$, we conclude that $B \times R$ and $A \times B \times R$ should not be pooled for the data from sources (1), (3), and (4). Even if we take $\alpha = .20$, we decide not to pool in the case of the data from source (3). Let us now look at this example in greater detail. The data represent yields (in bushels per acre) of corn in an experiment conducted to compare four methods of seedbed preparation and four methods of planting, using four blocks. The methods of seedbed preparation are the whole-plot treatments A, the planting methods are the subplot treatments B, and the blocks are the replications R. Since there are two fixed factors (A and B)

TABLE 3

ANALYSIS OF VARIANCE FOR DATA FROM SOURCE (3) ABOVE

Source of Variation	d.f.	S.S.	M. S.	F
Seedbed methods (A)	3	194.56	64.85	64.85/17.58 = 3.69
Replications (R)	3	223.81	74.60	
$A \times R$	9	158.25	17.58	
Planting methods (B)	3	4107.39	1369.13	1369.13/28.08 = 48.76**
$A \times B$	9	221.74	24.64	24.64/13.18 = 1.87
$B \times R$	9	252.72	28.08	
$A \times B \times R$	27	355.75	13.18	
Total	63	5514.22	—	

**Significant at the one percent level.

and only one random factor (R), the fixed main effects and interaction are tested by their interactions with the random factor, as shown in Table 3. Anderson and Bancroft give the correct test for the whole-plot treatments A, but test the subplot treatments B and the interaction $A \times B$ by the subplot error obtained by pooling $B \times R$ and $A \times B \times R$. In this case they reach the correct conclusions (B highly significant, $A \times B$ non-significant), but clearly this will not always be true.

4. *Strip Plots and Sub-subplots.*

The expected mean squares are different for strip-plot experiments than for ordinary split-plot experiments, but the same tests are appropriate (see, for example [4], [6]), and the same preliminary test for pooling can be used. The theory can also be extended in an obvious way to split-split-plot experiments. If it cannot be assumed that the whole-plot treatment A, the subplot treatment B, and the sub-subplot treatment C do not interact with replications, the sub-subplot error should be partitioned into four parts $C \times R$, $A \times C \times R$, $B \times C \times R$ and $A \times B \times C \times R$. In the most common case (A, B and C fixed, and R random), these are appropriate for testing C, $A \times C$, $B \times C$ and $A \times B \times C$ respectively. They should be pooled only if this is indicated by the results of appropriate preliminary tests of significance.

5. *Acknowledgments.*

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QUERIES AND NOTES

D. J. FINNEY, *Editor*

156 NOTE: Confidence Intervals for Recombination Experiments with Microorganisms

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1. METHODOLOGY

In a typical recombination experiment, a parent bearing a biochemical mutation at the A locus is mated with a parent bearing a biochemical mutation at the B locus, both loci on the same chromosome. The two parental types are thus $(a+)$ and $(+b)$. The loci (or markers) are usually identified with nutrient elements such as adenine or lysine, and a mutation at one of these loci signifies that the organism carrying the mutation will not grow unless the corresponding nutrient element is present in the growth medium. Progeny from such matings are of four types. If no recombination takes place on the chromosome between the loci, progeny must be of the parental types, and the two classes have equal expected frequencies. If a single recombination takes place in this region, the progeny will be $(++)$ or (ab) and these types likewise have equal expected frequencies. Types $(++)$ and (ab) are called recombinants and types $(a+)$ and $(+b)$ are called non-recombinants. Clearly the frequency of occurrence of recombinants is dependent on the distance between the loci, assuming that recombination is equally likely to occur anywhere along the chromosome, and obtaining information about distances between loci is one of the main purposes of a recombination experiment. The proportion of recombinants is called the recombination frequency and the proportion of the $(++)$ type is called the prototroph frequency.

Since, ordinarily, the four types of progeny cannot be separately identified, platings are made both on complete media (containing elements A and B) and on minimal media (A and B omitted). All four

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types will grow on complete media but only the prototroph (++) will grow on minimal media. Thus, if a count of x organisms is found by plating v_x *ml* of a suspension on a minimal medium and a count of y organisms by plating v_y *ml* on a complete medium, the prototroph frequency is estimated by

$$R = v_y x / v_x y.$$

If the total count, $S = x + y$, is large and neither x nor y is too small, a confidence interval can be computed from the formulas,

$$R_L = v_y(T - A)/v_x(1 + A), \qquad R_U = v_y(T + A)/v_x(1 - A) \qquad (1)$$

where R_L and R_U , respectively, are the lower and upper confidence limits, $T = x/y$, $A = t_\alpha(T/S)^{1/2}$, and where t_α is the normal deviate corresponding to a $100(1 - \alpha)$ percent confidence interval.

As a numerical example, consider an experiment that yielded the values $v_x = 180$, $x = 561$, $v_y = 2.5$, $y = 3759$ for which 95 percent confidence limits ($t_{.05} = 1.96$) are required. We have

$$R = \frac{(2.5)(561)}{(180)(3759)} = .002073$$

$$T = 561/3759 = .14924, \qquad S = 561 + 3759 = 4320,$$

$$A = 1.96(.14924/4320)^{1/2} = .01152,$$

$$R_L = \frac{(2.5)(.14924 - .01152)}{180(1 + .01152)} = .001891,$$

$$R_U = \frac{2.5(.14924 + .01152)}{180(1 - .01152)} = .002259.$$

These limits are not, in general, symmetrical about the estimate.

In many cases, the experimenter will have preliminary information about the expected orders of magnitude of the ratios x/v_x and y/v_y and may want to know how large an experiment is required to yield a reasonably precise estimate of the prototroph frequency. One measure of the precision is the relative width of the confidence interval,

$$W = (R_U - R_L)/R.$$

Ordinarily, one is interested in relative widths of not more than 30 percent ($W \leq .30$), and in this case the relation,

$$S = 4t_\alpha^2(1 + T)^2/TW^2, \qquad (2)$$

holds approximately. Both the total count S and the ratio of the counts T, are important in determining the precision of the estimate,

and it can be shown that if the counts are in a 1 : 1 ratio, the total count required for a specified relative interval width will be a minimum. With this in mind, if we put $T = 1$ in (2), the total count required is given by

$$S = 16t_\alpha^2/W^2. \tag{3}$$

Thus the procedure is to decide on the confidence level and interval width desired and to calculate the total count from (3). Then, knowing that the counts should be in a 1 : 1 ratio and having preliminary information about x/v_x and y/v_y, the amounts to be plated out can be calculated directly. If the amounts calculated turn out to be experimentally unfeasible, one might have to depart from a 1 : 1 ratio for the counts, in which case, the total count can be calculated from (2) for whatever value of T is found to be acceptable. Some trial and error with the use of (2) may be necessary in these cases.

As an example, consider a situation in which it is expected that the counts from a standard suspension will be about 2 per *ml* for x and 5,000 per ml for y. A relative width of about 20 percent is desired for a 95 percent confidence interval. Thus $t_\alpha = 1.96$, $W = .20$ and

$$S = 16(1.96)^2/(.20)^2 = 1540,$$

whereupon the amounts to be plated should be chosen so that approximately 770 counts will be obtained from the platings on each medium. In other words, $v_x = 770/2 = 385$ and $v_y = 770/5{,}000 = 0.15$ are the amounts to be plated on minimal and complete media, respectively.

Although sample sizes determined by this method may be used as a rough guide in designing recombination experiments, they should not be regarded as optimum. Readers interested in statistically more sophisticated procedures for determining sample sizes should refer to Birnbaum [1954].

2. DERIVATION

Since v_x and v_y are known constants, the statistical problem consists of finding a confidence interval for the parameter $\theta = \mu/\nu$, where $\mu = E(x)$ and $\nu = E(y)$. Assuming that x and y are independently distributed Poisson variables, Birnbaum [1954] showed that a confidence interval for θ may be constructed by treating $p = y/(x + y)$ as a binomial variable with $E(p \mid x + y) = \pi = \nu/\mu + \nu$. Limits on π, say (π_0, π_1), are easily obtainable from published tables of the binomial distribution, whereupon limits on θ are given by

$$\theta_0 = (1/\pi_1) - 1 \quad \text{and} \quad \theta_1 = (1/\pi_0) - 1.$$

In many cases, however, $x + y$ is large and the normal approximation to the binomial distribution may be used to calculate the limits on π, providing π is not near zero or one. This in turn leads to the limits given in (1).

The relative width of the confidence interval for the prototroph frequency can be written as

$$W = W_\pi(1 + T)/T[1 - (W_\pi^2/4)]$$

where $W_\pi = (\pi_1 - \pi_0)/p$, the relative interval width for π. In most practical situations W_π will be small, say $\leq .30$, in which case $W \cong W_\pi[1 + (1/T)]$. When the substitution is made for W_π, the result can be expressed as in (2). For fixed W, this expression has a minimum at $T = 1$, and (3) follows directly. I am indebted to the referee for pointing out that if $W \leq .30$, W_π will be about half as large as W when $T = 1$, and the approximation will be even better than indicated.

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157 NOTE: Estimation of Proportion from Zero-truncated Binomial Data

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INTRODUCTION

An important problem of estimation arises, chiefly in genetical contexts, when the proportion of individuals bearing some particular character must be estimated from the frequencies observed in a random sample of groups or families which have at least one individual bearing this character. The estimation by maximum likelihood of the proportion p in this situation has been discussed principally by Haldane [5], [6], Fisher [3] and Finney [2].

In conjunction with D. G. Catcheside's studies on tetraploid maize [1] the author derived an iterative procedure, which is presented here, with a simpler mathematical form and rather better convergence properties

than the standard method based on score and information, which is described by Finney [2].[1]

It was found preferable to estimate, instead of p, a parameter M related to p by the equation $X/M = p$, where X is the total number of character-bearers in the sample. The parameter M may be thought of as the total number of individuals that might have been observed if families with no character-bearers had also been ascertained in the sample. In this respect the method described here is a special case of the general method given by Hartley [7], in which the application of maximum likelihood to data with missing (or coalesced) classes is facilitated by estimation of the relevant frequencies for those classes. A similar approach has also been used by Fyfe [4].

The formula given below, however, leads to less computation than Hartley's procedure, when several different sizes of family are involved. In the present instance accelerated convergence has been obtained by applying Newton's method of approach by tangents to the solution of the equation $M = M^*(M)$, and requires, for each cycle of computation, only a simple iteration in this equation. Hartley, on the other hand, employs the "approach to the geometric limit", which differs from Newton's method in that approximating chords are used in place of tangents, and thus requires *two* basic iterations in each cycle.

THE ITERATION FORMULA

The basic sampling distribution is the zero-truncated binomial. Accordingly, the likelihood function for the data, using the notation given in Table 1, is essentially

$$L = X \log p + (N - X) \log q - \sum_{s \geq 2} f_s \log (1 - q^s). \qquad (1)$$

If $M = X/p$, $m_s^* = n_s/(1 - q^s)$, and $M^* = \sum m_s^*$, the differential coefficient of the likelihood function with respect to M, may be expressed in the form

$$\frac{dL}{dM} = -\frac{p}{Mq}(M - M^*). \qquad (2)$$

---

[1] In Finney's paper it is suggested, with reference to the tables of scoring functions provided, that linear interpolation may be used to obtain more accurate approximations to the maximum likelihood value $\hat{p}$. As a matter of principle it may be noted that *linear* interpolation is insufficient for this purpose. Linear interpolation, between the entries for p_1 and p_2 say, will determine an estimate intermediate to the two estimates based on p_1 and p_2 respectively, but generally the latter estimates will both lie on the same side of the maximum likelihood value $\hat{p}$, even when p_1 and p_2 are themselves on opposite sides of $\hat{p}$. More accurate interpolation, based on second differences as well, is therefore necessary.

The factor p/Mq is essentially non-zero. Application of Newton's method, in which the successive approximations to the zero of $f(x)$ are given by the formula

$$x_{k+1} = x_k - [f(x_k)/f'(x_k)],$$

to the factor $(M - M^*)$ gives the formula

$$M_{k+1} = (M_k^* - r_k M_k)/(1 - r_k), \tag{3}$$

where

$$r = \frac{p}{Mq} \sum_{s \geq 2} \frac{m_s^*(m_s^* - n_s)}{f_s}.$$

TABLE 1

NOTATION

Size of group, s	Frequency	Number of individuals	Number of character-bearers
2	f_2	$n_2 = 2f_2$	x_2
3	f_3	$n_3 = 3f_3$	x_3
...	...	...	...
s	f_s	$n_s = sf_s$	x_s
...	...	...	...
Total	F	N	X

Estimation is completed by determining $\hat{p}$ as the proportion of X to $\hat{M}$, and the amount of information in relation to p may then be determined as

$$I_p = \frac{M}{pq}(1 - r), \tag{4}$$

evaluated at the point of maximum likelihood. The amount of information differs from that for simple binomial data by the factor $(1 - r)$. The factor r thus emerges as the *relative* amount of information lost by truncation in the sample. This factor governs the rate of convergence of the iterative process, convergence being extremely rapid when r is small. Even when the loss of information is as high as 40 percent, however, as in the example below, a single cycle of computation, from a suitable starting point, will give a high degree of accuracy.

A very good starting point is provided by the (iterative) solution of the much simpler equation

$$M = N/(1 - q^F), \tag{5}$$

where $\bar{s}$ is the mean size of families observed, or the equivalent equation for the Poisson distribution (if p is small), as used by Fyfe [4]. Indeed for many practical purposes the solution of (5) will itself be sufficiently accurate. In the example given below, in spite of the wide range of family sizes, the solution of (5), roughly $M = 3{,}300$, is within 3 percent of the correct maximum likelihood value, and, in the case of the data on human albinism discussed by Haldane [6], the relative error is 4 percent.

EXAMPLE

Catcheside [1] gives the numbers of recessive *su* seeds observed on 24 cobs from tetraploid maize triplex for *su*—1$^+$ and pollinated by nulliplex. It was possible that the parent plants of one or more of the seven cobs observed with no *su* seeds might have been quadruplex

TABLE 2

ITERATIVE SOLUTION OF THE EQUATION $M = M^*(M)$

$s_x = n_x$	x	q_0^*	m_{x0}^*	q_1^*	m_{x1}^*
18	1	.7935	87.2	.83749	110.76
65	2	.4338	114.8	.52707	137.44
74	1	.3864	120.6	.48235	142.95
76	1	.3766	121.9	.47294	144.20
84	2	.3399	127.2	.43709	149.22
86	2	.3312	128.6	.42856	150.50
131	2	.1858	160.9	.27508	180.71
140	3	.1655	167.8	.25174	187.10
173	2	.1083	194.0	.18187	211.46
181	2	.0977	200.6	.16808	217.57
188	2	.0893	206.4	.15688	222.98
206	1	.0709	221.7	.13139	237.16
211	1	.0665	226.0	.12507	241.16
219	2	.0600	233.0	.11559	247.62
223	4	.0570	236.5	.11112	250.88
251	3	.0398	261.4	.08433	274.12
259	2	.0359	268.6	.07794	280.89
$N = 2585$	$X = 33$	$M_0^* = 3077.2$		$M_1^* = 3386.72$	
$S = \sum m_x^* (m_x^* - n_x)/f_x$ (all $f_x = 1$, $F = 17$)		$S_0 = 73{,}842$		$S_1 = 142{,}276$	
		$r_0 = 0.3694$		$r_1 = 0.41850$	
		$1 - r_0 = 0.6306$		$1 - r_1 = 0.58150$	
$M_0 = 2585$		$M_1 = 3{,}366$		$M_2 = 3{,}401.63$	
$p_0 = 0.012766$		$p_1 = 0.009804$		$p_2 = 0.009701$	

rather than triplex. As a check, therefore, p was estimated from the 17 cobs with one or more *su* seeds. The iterative calculations for these data are set out in Table 2, and give an estimate $\hat{M} = 3402$ in very close agreement with the actual number of seeds observed, 3359, on all 24 cobs. The sensitivity of the data on this point is rather low, however, as the relative standard error of $\hat{M}$ (and $\hat{p}$), determined by formula (4), is 23 percent.

To exhibit the convergence properties, and for comparative purposes, $M_0 = N = 2585$ has been chosen as the starting point for the computations in Table 2. In practice the value 3359 might have been chosen, or, lacking this information, the approximate solution 3300 of the simpler equation (5). A single iteration would then have given far more accuracy than actually required. The values of q^* were determined in this instance by logarithmic calculation, but this calculation can be avoided if suitable binomial tables are available. The values r_s are determined essentially by the computation of a weighted sum of products of the m_s^* with the differences $m_s^* - n_s$ (not shown).

To compare rates of convergence the successive approximations to the solution of $dL/dp = (M - M^*)/q$, by adjustment in terms of score and information, were also determined. The comparison is shown in Table 3. It can be seen that the present method does very much better from a poor start than the other, requiring only one iteration instead of two. However the disparity diminishes, as one would expect, in the neighbourhood of the maximum likelihood value.

TABLE 3

SUCCESSIVE APPROXIMATIONS TO $\hat{M} = 3401.76$ BY APPLICATION OF NEWTON'S METHOD TO THE EQUATIONS (i) $M = M^*(M)$, (ii) $dL/dp = 0$. RELATIVE ERRORS ARE SHOWN IN PARENTHESES

	M_0	M_1	M_2	M_3
$M = M^*$	2585	3366 (1%)	3401.63 (0.004%)	3401.76 ($\hat{M}$)
$dL/dp = 0$	2585	3697 (10%)	3421.19 (0.6%)	3402.04 (0.008%)

COMMENT

The approach which led to the present method was somewhat different from Hartley's and may be of interest in other connections. In the simplest cases the differential of the likelihood function with respect to a parameter (or some related parameter), θ say, can be factorized

into two parts, one linear in θ and the other essentially non-zero. More generally,

$$dL/d\theta = g(l(\theta, x)).h(\theta, x)$$

where $l(\theta, x)$ is linear in θ, $g(0) = 0$, and $h(\theta, x)$ is essentially nonzero. In such cases one has the explicit solution given by the zero of $l(\theta, x)$ and no iteration is necessary. It was argued that, in the less simple cases, a similar factorization might be sought, in which $l(\theta, x)$, though not strictly linear, was in some sense asymptotically linear. In the present instance, for example, the function $M - M^*$ is asymptotically linear in M as $\bar{x} = X/F$ increases. A sketch graph of this function is shown in Figure 1. Curvature of the function is restricted by a tangent

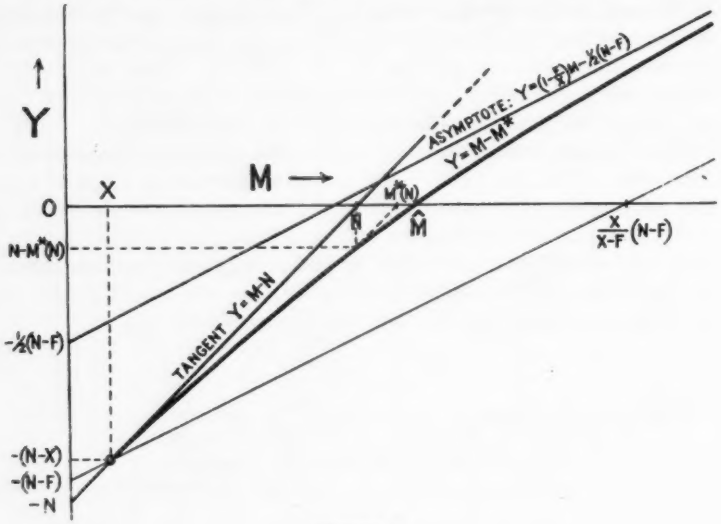

FIGURE 1

SKETCH GRAPH OF THE FUNCTION $M - M^*(M)$

(The intercept $X(N - F)/(X - F)$ corresponds to Haldane's estimate of p, [6], from data in which the probability of ascertaining a family is proportional to the number of affected individuals in the family.)

and an asymptote which differ in slope only by the factor $1/\bar{x}$. Generally, it could be expected that iterative methods applied to $l(\theta, x)$ rather than to $dL/d\theta$ would give more rapid convergence, as the functions g and h in the latter will generally have an adverse effect on convergence by increasing curvature. The comparison is complicated, however, by the presence of one or more inflexion points in $dL/d\theta$.

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BOOK REVIEWS

J. G. SKELLAM, *Editor*

Members are Invited to Suggest Books for Listing or Review to the Editor

7 GUMBEL, E. J. **Statistics of Extremes.** New York: Columbia University Press, 1958. Pp. xx + 375. $15.00.

B. F. KIMBALL, *New York Public Service Commission, New York, N. Y., U.S.A.*

This work is essentially a source book on the statistics of extreme values. Furthermore it is the only source which is comprehensive. Viewed as a source book it is well arranged and well documented. The bibliography includes over 600 books and articles, to which specific references are made throughout the book. Of these, 34 are papers by the author, or written in collaboration.

The first chapter deals with definitions and the basic concepts. In the second chapter, on *order statistics*, the theory of *exceedances* is set forth and handled in a straight-forward and concise manner.

In Chapter 3 the exact distribution of the extreme values of a sample are introduced. Chapter 4 is given over to an analysis of the exact distributions of extremes, pointing out the essentially different types which are important.

These first four chapters comprise nearly half the subject matter and include all the material dealing with "exact" distributions of extreme sample values. Perhaps the principal advances in the study of the distribution of extremes in the last twenty five years have been brought about by recognition that the asymptotic forms of these distributions are usually adequate as approximations to the exact distributions in the applied field, and are much simpler to deal with.

The asymptotic forms fall naturally into three classes, of which the doubly exponential is of the most consequence since it is the asymptotic form which results from a universe having an "exponential" type of cumulative distribution function, such as the logistic, normal and Gamma distributions. A second class, or "second asymptote" as referred to by Gumbel, stems from distributions of the Cauchy or Pareto type. The third class is often referred to as Weibull's distribution when used for the lower extreme. Both can be obtained from the first by suitable logarithmic transformations. The first "asymptote" and its applications are discussed in Chapters 5 and 6, covering about 100 pages. This class is of particular interest to biologists—for example, in studying extinction times of bacteria[1]. The second and third asymptotes are treated in Chapter 7. Chapter 8 is devoted to the asymptotic forms of the range and mid-range, and their applications.

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[1] *Statistical Theory of Extreme Values and Some Practical Applications*, U. S. Dept. of Commerce N. B. S. Applied Math. Series 33(1954) p. 43; U. S. Gov. Printing Office, Washington, D. C. 40c.

This reviewer finds the author very ingenious in deriving methods which he believes will facilitate application of the theory to practical problems. Some of these ingenious devices are open to criticism. For example, the discussion of the topic *Fitting Straight Lines on Probability Papers* (pp. 34–36) is more ingenious than logical.

A formula is developed at the bottom of page 23 for the probability that a return period T will be reached in v trials. This probability is "distribution free" and for large T can be approximated by $W(v) = 1 - \exp(-v/T)$. From this Gumbel develops what he calls a "control interval".

$T/\lambda < v < T\lambda, \lambda > 0$, the probability that v will lie on this interval being given by $P = e^{-1/\lambda} - e^{-\lambda}$. This is ingenious, but, since the probability density function is monotonically decreasing from $v = 0$, the shortest interval carrying the same probability would be $0 < v < T\lambda'$ with $P = 1 - e^{-\lambda'}$. Hence, for $P = .6827$, $\lambda' = 1.148$ and the "control interval" would be $0 < v < 1.148T$ rather than $(.3196)T < v < (3.129)T$.

A similar criticism applies to the control intervals (5) on page 215. These intervals are centered at the mode. The "shortest" such interval for $P = .6827$ would be given by $\Delta = -.917$, $\Delta = +1.317$, rather than by $\Delta = \pm 1.141$. This would change (8) to $T(y + \Delta) = 3.732T(y) - 1.366$, $T(y - \Delta) = 0.400T(y) + 0.300$. Likewise for $P = .9545$, $\Delta' = \pm 3.0069$ becomes $\Delta' = -1.59$ and 3.251. Thus, when the underlying distribution is asymmetrical, some adjustment should be made when possible.

In presenting *The Extreme Control Band* of Table 6.1.6, p. 218, and in other references to the control band, besides noting the lopsided character of the "shortest interval" of fixed probability, the author might have pointed out that most of these formulae presume a *correct* estimate of the scale parameter α. As I pointed out in my contribution to the book, the uncertainty of the estimate of α will involve the variance as a function of y, the distance from the mode, and N, the size of the sample used in determining α [cf. (2) p. 235]. Thus the complete variance upon which a confidence band should be based will involve both the "variance of position" of the fitted line and the intrinsic variance of the order statistic (used as a basis for Table 6.1.6.)[1].

Other formulas for the "variance of position" are casually referred to, such as the "Control Curve of Dick and Darwin", Section 6.1.7; and formula (5), p. 228, which gives the sampling variance of an estimate x obtained by the method of moments. In using this latter formula it should be made clear that the σ^2 in the denominator refers to the variance of the sampled values and hence might be replaced by s^2. The formula (6) which follows it would appear to be in error. With $(\pi^2/6)/\alpha^2$ substituted for σ^2 and $\sigma^2(y) = \alpha^2\sigma^2(x)$ the α^2 should cancel out. Also the significance of (6) is not clear since y is usually *assigned* a value in making an estimate from (4) by the method of moments.

The matter of the identification of the variance of the order statistic vis à vis that of the sampling variance of the estimate (variance of position) needs to be made clearer.

I have noticed only two rather obvious typographical errors: On p. 24, line 6, .4637 should be replaced by .04657, and on p. 215, line 1, .05450 should be replaced by .95450.

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[1] Henry Schultz, The standard error of a forecast from a curve. *J. Amer. Stat. Asso.* **25** (1930), 139–85.

8 VESSEREAU, A. **Méthodes Statistiques en Biologie et en Agronomie**, Tome deuxième. Paris: J.-B. Baillière et Fils, Editeurs. Nouvelle edition entièrement refondue, 1960. Pp. 540. 55 NF.

P. ROBINSON, *Canada Department of Agriculture, Ottawa, Ontario, Canada.*

This book, as the title implies, is intended principally for research workers in the biological sciences. There are now several good texts available in English, but there are few in the French language. In his introduction to the first edition the author says "Le présent ouvrage se propose de combler cette lacune." That there was this need may perhaps be judged by the short time elapsing between the first and second editions. The second edition has been completely revised and now includes—

(i) a fuller discussion of the underlying mathematical reasoning,
(ii) a more general description of the analysis of variance.
(iii) a more extensive treatment of experimental design, including confounding, and
(iv) tables and graphs relating to the binomial and Poisson distributions.

This book contains a great deal of useful information and the mathematical treatment is kept simple throughout. Basic ideas on probability and sampling are discussed in the first four chapters, simple tests of significance in the next two chapters, experimental design in the next nine, and regression and correlation in the last two.

In covering such a wide field within the confines of a single book, any treatment in depth is of course precluded. The broad approach to the subject may have led the author to include descriptions of higher order moments, the β_1 and β_2 measures of skewness and kurtosis, and Sheppard's corrections. These, however, are completely unnecessary in an introductory text of this nature intended for the biologist, as is evidenced by the fact that they do not reappear after Chapter II. It is also a pity that outdated measures of dispersion—the probable error (pp. 56 and 100) and the mean error (p. 100)—are discussed. These are interesting from a historical viewpoint, but only serve to confuse the agricultural worker.

It would have been better to sacrifice breadth of approach in these areas in order to deal a little more fully with problems of more direct concern to the biologist. In particular the sections on transformations, split plots, and the combined analyses of repeated experiments could have been expanded. A discussion on expected mean squares might have helped when dealing with this last problem; the correct choice of the appropriate error for testing a particular hypothesis would then have been clearer, instead of appearing to be left to the whim of the experimenter (p. 419).

A fuller discussion of the difficulties involved in multiple comparisons would also have been helpful. Comments (2) and (3) on pp. 187 and 188, for example, appear to be contradictory, and the discussions on pp. 203, 204, 206 and 216 could be misleading.

The use of artificial data in certain illustrations (pp. 193, 458) is unwarranted when so many examples are now available. This is particularly dangerous when dealing with the analysis of covariance because the interpretation can be tricky. The author's suggestion of circumstances in which a covariance analysis could be used—p. 451—"Lorsqu' on étudie l'influence des engrais sur l'indice de pureté du sucre extrait d'une culture de betterave sucrière, les résultats dépendent du poids

des racines, qui n'est pas constant dans les différentes parcelles de l'essai, mais qui peut être mesuré après coup"—is a particular case in point.

Finally I must disagree with a piece of advice which the author gives in his "En guise de conclusion." He suggests, if there is any doubt in the mind of the research worker as to the applicability of some of the techniques discussed, that "mieux vant encore s'en tenir aux schémas éprouvés." This value of this advice depends entirely upon what is meant by "schémas éprouvés". In general, it would be far better to advise the research worker "de demander conseil aupres des experts en statistiques."

LOVE, A. G., HAMILTON, E. L. and HELLMAN, I. L. **Tabulating Equipment and Army Medical Statistics,** Washington, D. C.: Office of the Surgeon-General, U. S. Army Medical Service, 1958. Pp. x + 202. 36 Figures. $2.00.

W. W. Holland, *London School of Hygiene and Tropical Medicine, London, England*

This is a delightfully written account of the development of machine methods and of the techniques of recording in the American Army. The book not only traces the development of statistical services, but also shows how great the dependence of an efficient military medical service is on the collection, tabulation and assessment of data. After reading this short monograph it is easy to understand how the excellent description of such diseases as cholera, respiratory infection and of injuries sustained by American Army personnel during the two World Wars could be completed. It is of interest to read that, even in the first years of the existence of the American Army, during the Napoleonic Wars, acute respiratory disease was a severe problem. Although the treatment tends, at times, to be somewhat too biographical, a good account of the development of punch cards, sorting and tabulating systems and of computers is given. Full details and illustrations of the various forms used for recording data are described as well as an account of the collection and analysis of anthropometric information obtained during routine assessment of personnel on enlistment and discharge.

ABSTRACTS

The following are abstracts of papers presented at the annual meeting of the Biometric Society ENAR, held jointly with the Biometric Society WNAR, the American Statistical Association, and the Institute of Mathematical Statistics in Stanford, California on August 23 to 26, 1960. Abstracts of additional papers presented at this meeting appear in other society publications.

683 KLAUS ABT (U. S. Naval Weapons Laboratory, Dahlgren, Va.). **Analysis of Variance of Differences Versus Analysis of Covariance.**

In analyzing paired data $(x; y)$, classified in one or more directions, where x and y are observations of the same variable (and therefore usually observed at different times) at least two methods are available. First there is the analysis of covariance in which y is considered to be stochastically dependent on x, the "independent" variable. A second method is the analysis of variance of the generalized differences, $d = y - \beta_0 x$, briefly called "analysis of differences". The case $\beta_0 = 1$ represents the most important case of ordinary differences.

It is shown that, if the condition $E(b_E) = \beta_0$ is satisfied ("expectation of the coefficient of error sum of squares regression line equals β_0", which easily can be tested), the analysis of differences has a power equal to or even higher than that of the analysis of covariance. From many calculated examples, it seems that the condition mentioned is satisfied quite often. In many cases, therefore, the analysis of differences will be the appropriate method for the data to be analyzed, besides this including a minimum of computation.

684 R. L. ANDERSON (North Carolina State College, Raleigh, N. C.). **Recent Developments in Multivariate Analysis.**

One of the most important recent developments in multivariate analysis has been the publication of some excellent textbooks on the subject, on both theoretical and applied aspects. This paper is in the nature of a discussion of what the writer feels is needed to improve multivariate techniques. The chief need is much more attention being paid to construction of experimental models, usually involving two or more equations, and methods of estimating parameters in these models, assessing their usefulness and testing hypotheses concerning them. Particular attention is paid to causal chains and to dynamic systems. For the latter, methods based on lagged dependency models and Laplace transform techniques are indicated.

Some possible weaknesses of current multivariate analysis of variance procedures are indicated. Problems which should be studied in the following fields are outlined: discriminatory, canonical, factor and component analysis. Special attention is focused on the construction of selection indexes, and the selection of predictors in ordinary multiple regression analyses.

685 ROLF E. BARGMANN (Virginia Polytechnic Institute, Blacksburg, Va.). **On the Problem of Ordering Variables in Tracing Significant Contributions.**

After rejection of some general linear hypothesis in multivariate analysis it is frequently desirable to ascertain how much each variable contributes to the observed differences. The step-down procedure—i.e., a process analogous to analysis of covariance in which we study the first variable, the second given the first, the third given the first and second, etc.—depends on the ordering of the variables. The present report discusses the use for this purpose of the correlations of a linear discriminant function $a'X$, where a' is the eigenvector associated with the largest root of HE^{-1} (H = matrix of S.S. and S.P. due to hypothesis, E same due to error). A similar procedure is described for the discrimination of common factors, i.e., for those cases where any difference between groups is supposed to be in terms of those artificial components only which are shared by two or more of the observable variables. A detailed demonstration study will be presented for illustration.

686 EDWARD C. BRYANT and DONALD W. KING (University of Wyoming, Laramie, Wy.). **Estimation from Populations Identified by Overlapping Sampling Frames.**

Consider a population of unknown size identified by p sampling lists, each with M_i entires from which independent samples of size m_i, $i = 1, 2, \cdots, p$ may be drawn. It is assumed that the sampling procedure will reveal which of the p lists contain the individuals interviewed. An estimate of the total number in the population is desired, as well as the number of individuals appearing on each possible combination of sampling lists. Maximum likelihood and minimum modified chi square estimates are considered. By moderate restrictions, an approximation to the variance is provided by use of the Taylor's series expansion around the expected numbers in each category of listing combinations.

687 BRADLEY E. COPELAND (New England Deaconess Hospital, Boston, Mass.). **Problem in Pathology With Statistical Aspects.**

The pathologist in his role in diagnostic laboratory medicine finds a compelling need for a broader comprehension of the fundamental principles of statistics for himself and on the part of the practicing physician, the medical technologist, and the medical research worker.

Every physician must be equipped with certain statistical tools to properly utilize the laboratory measurements now available to him for diagnosis and treatment.

There must be clear and rapid communication between the pathologist and the clinician concerning the variation in normal values and the reliability and inherent variability of laboratory measurements.

The first major problem relates to the barrier of statistical nomenclature and the multiplicity of statistical formulas. Communication cannot be successful until pathologists and clinicians learn to handle with ease such fundamental statistical concepts as standard deviation, standard error, variance, the t test, and the F ratio.

Since medicine is concerned with the individual, there is a need to clearly identify the tools which separate the diseased individual from a normal population as opposed to the tools which differentiate normal and abnormal populations. Both are useful devices, but they are the source of much confusion in the minds of physicians.

Currently there is an also pressing need for more comprehensive definitions of normal values in all laboratory measurements—normal as regards variation in age, sex, geographical location, and any other environmental or hereditary factor which may influence the normal population.

To achieve permanent indoctrination of the medical profession with useful statistical tools is a necessary and useful goal. It is in this area that active communication between pathologists and statisticians should take place to develop solutions to the problems described.

688 R. C. ELSTON (University of North Carolina, Chapel Hill, N. C.). **On Additivity in the Analysis of Variance.**

The problems of testing for non-additivity and of finding the best transformation of the data to minimize it are discussed. Consider the model: $E(y_q) = \mu + \mu_q + c\mu_q^2$, where y_q is an observation belonging to the q-th subclass in an analysis of variance problem. If this model fits our data, and if $\max \mu q - \min \mu q < 1/|c|$ (the range over which this model is a strictly monotonic function of μ_q), then there exists a useful transformation of our data that will give additivity; that is the transformed data will be fitted by an additive model. Two tests that have already been proposed for testing for non-additivity are tests of the null hypothesis $c = 0$ against $c \neq 0$ under models that can be considered as approximations to the above model. It is shown how estimates of μ and c can be used as guides in finding an appropriate transformation of the data.

689 WALTER T. FEDERER (Cornell University, Ithaca, N. Y.). **Augmented Designs with Two-, Three- and Higher-Way Elimination of Heterogeneity.**

Augmented experimental designs are standard ones to which additional treatments have been added. The additional treatments may or may not be replicated the same number of times as the treatments in the standard design or the same number of times as other new treatments. The groupings of treatments into rows, columns, complete blocks, etc. may be such that the size of the group is or is not equal. Construction procedures, randomisation procedures and the analyses in general form have been presented for augmented experimental designs with two-, three- and higher-way elimination of heterogeneity.

690 WILLIAM R. GAFFEY (California State Department of Public Health). **Tests of Hypotheses Concerning Boundedness in Convolutions.**

Suppose the random variable Y, with unknown d.f. $G(y)$, is observed subject to error, so that $X = Y + Z$ is the random variable actually observed. Let $H_s(s)$ be the (known) conditional d.f. of the continuous "error" random variable Z, and let $F(X)$ be the d.f. of X. We are concerned with deriving tests of the following two-hypotheses about the distribution of the "true" random variable Y; (1) $G(y) = 0$ for $y < a$, and (2) $G(y) = 1$ for $y > b$.

Under suitable restrictions on the form of $H_s(s)$, it turns out that hypothesis (1) is true if and only if $F(X) \leq H_s(x - a)$ for $x < a$, and hypothesis (2) is true if and only if $F(X) \geq H_s(x - b)$ for $x > b$. A test of either inequality is therefore a test of the corresponding hypothesis about $G(y)$.

A test is proposed using the one sided Kolmogorov-Smirnov statistic, restricted

to the appropriate portion of the range of X. The large sample distribution of the statistic is derived, and the consistency of the test is established.

691 MAX HALPERIN (General Electric Co., Schenectady, N. Y.). **Nearly Least Squares Estimates in Heteroscedastic Regression.**

Suppose we have observations y_{ij}, $i = 1, \cdots, k$, $j = 1, \cdots, n_i$ where $Ey_{ij} = a + bx_i$ and $\text{Var } y_{ij} = \sigma_i^2$, the x_i are presumed known, and the y_{ij} are normally distributed, mutually independent, and $k > 2$, $\min n_i > k$. In this paper we show how to generate estimates of a and b which are nearly least squares in the sense that the correlation of the estimates is identical to that which would be obtained from a least squares fit with known variances while the variance of the estimates differs from that appropriate to the known variance least squares fit by a multiplicative factor which approaches unity as $\min_i n_i \to \infty$ and k remains constant. The procedure further allows estimation of the covariance matrix of the estimates with $(\min_i n_i - k + 1)$ degrees of freedom and hence an exact confidence region for a and b based on Hotelling's T^2 distribution. The results cited are of a conditional nature in which the conditioning constrains the variance multiplying factor referred to above. The distribution of the multiplicative factor aside from known constants is that of Hotelling's central T^2 in general (Student's "t" if $k = 3$). As a consequence, alternative exact confidence intervals of unconditioned nature are available in principle by averaging the conditional results over the appropriate distribution. It is conjectured that matching moments to determine approximate degrees of freedom for an "equivalent" T^2 distribution is adequate from a practical point of view. If $k = 2$, the procedure we propose gives estimates with exactly least squares variances and exact confidence intervals or regions. It is conjectured that results similar to the above generalize to general polynomial or polyvariable regression linear in the parameters and a sketch of the type of argument is given.

692 R. C. HENNEMUTH (Inter-American Tropical Tuna Commission). **Estimating Vital Statistics of Yellowfin Tuna Populations.**

Knowledge of vital statistics is essential to the study of the dynamics of exploited fish populations; age composition, growth rate and mortality rates being particularly important.

Determination of age of yellowfin tuna by using marks on scales or bones has not proven reliable; however, growth rate and relative age have been estimated by observing the temporal changes in the size composition of catch. Absolute age has been approximately determined by comparing the average time of spawning with the time and size at which the age groups initially appear in the catch.

Total mortality rate has been estimated by analyzing catch-curves of successive year classes, which have been computed from age composition and indices of apparent abundance based on catch per unit effort data.

693 BURTON J. HOYLE and GEORGE A. BAKER (University of California, Davis, Cal.). **Game Theory Applied to Field Trials.**

The determination of the proper variety of a cereal to grow may be considered as a game with the Grower as one opponent and Nature as the other. A game matrix of forty-one independent yield trials on nine strains of Hannchen barley is presented. The trials cover three years and very diverse designs and environments

within the years. A similar but more restricted matrix for kernel weight is also presented. The whole structure of field trials is made clear by a contemplation of these game matrices. Sometimes one strain does better and sometimes another. That is, it is doubtful that there is a best strain. Sometimes all strains are close together and sometimes the strains differ widely. Some strains are very erratic, in relative yield, and some are very consistent. Strains highest with respect to yield are not necessarily good with respect to kernel weight and other desirable properties so over-all ratings involve weighting considerations on various characteristics.

It is clear from dominance considerations that some strains should seldom or never be grown. In other cases mixtures of strains may be better than any one strain.

A determination of the odds for the different strains depends on the distribution of nature's strategies.

694 AUGUSTUS C. JOHNSON (Booz-Allen Applied Research, Inc.). **A Stochastic Model of Incubation-Period Distributions.**

An independent-action birth-death model of infection is presented, based on the hypothesis that each organism has probability $\lambda\, dt$ of dividing and $\mu\, dt$ of dying during the time interval dt. λ and μ being constants. Incubation terminates when a colony reaches a lower absorbing barrier at o or an upper absorbing barrier at some number N, at which point a sign or symptom appears.

The resulting differential-difference system is solved to give expressions for the distribution of conditional probability that n organisms will grow to an upper absorbing barrier N between times o and t. Expressions for the moments are derived both from the distribution and directly, being exhibited explicitly for moments through the third.

695 CECIL L. KALLER and VIRGIL L. ANDERSON (Purdue University, Lafayette, Ind.). **An Environmental Extension of Chromosome Analysis in Population Genetics.**

A phase model has been developed for the special case of a diploid diallelic genetic population having K pairs of chromosomes in genetic equilibrium which are influenced by Q tri-level environmental factors. The theoretical structure for this development is based on the theory of factorial experimental designs with each of the $K + Q$ factors having three "levels." Estimates of the parameters of the population described by this model are obtained by extending the methods presented in a thesis by McKean (Purdue, 1958). This sampling method involves the formulation of a "chromosome population" by the random selection of a set of K chromosome pairs from the original genetic population. The chromosome pairs so drawn are combined to form all possible genotypes; individuals of each resulting genotype are placed in all 3^Q possible environmental level combinations in numbers proportional to their theoretical frequency. Under the assumption that all interactions involving three or more factors are zero, an analysis scheme is developed for the estimation of chromosome population parameters. Therefrom, by the relationship demonstrated between the chromosome population parameters and the corresponding parameters of the original genetic population, conditions are established under which these latter are estimable.

696 MARVIN A. KASTENBAUM (Oak Ridge National Laboratories, Oak Ridge, Tenn.). **Countercurrent Dialysis—A Stochastic Process.**

Peptides isolated from rat liver microsomes may be separated from contaminating amino acids, sugars and salts by countercurrent dialysis. A single such dialysis can achieve only fractional purification. Therefore, more complex systems of multiple dialysis, in which a linear series of cells are used, have been devised. The system of immediate interest may be described as follows: Let each dialysis cell be a stage, and each dialysis period be a cycle. Then after each cycle, the dialout (the solution outside the dialysis sac), at each stage is concentrated and used as the dialin (the solution inside the dialysis sac) in the succeeding stage, whereas the dialin at each stage is concentrated and returned to the dialysis sac of the previous stage. The dialin at the first stage is retained at the first stage, and the dialout at the final stage is taken out of the system. In the nomenclature of stochastic processes, the first stage represents a reflecting barrier and the last stage an absorbing barrier.

To determine the probability with which a particle of the isolate will be at a specified stage in the system after a given number of cycles have been carried out, the system is described in terms of a Markov process with a stochastic matrix resulting from the product of two matrices, namely, a diffusion matrix and a transfer matrix, and algebraically explicit solutions are derived for any number of stages and cycles.

697 JOSEPH KEILIN (U. S. Dept. of Health, Education, and Welfare, Washington, D. C.). **The Use of the Information Statistic as a Measure of Conformity in Comparing Two Sets of Responses.**

A morbidity survey of the city of Nashville and suburbs was recently conducted by the Air Pollution Medical Program. In order to obtain some measure of the reliability of responses a subsample was chosen for reinterview.

Two methods of looking at the data are discussed and two functions are proposed for measuring the proportion of information transmitted from the ordinal interview. The two methods dictate different null hypotheses and these in turn lead to the two different functions.

The results from the reinterview are presented and show relatively low amounts of information transmission. Further analysis of the data, using information theory procedures, is suggested.

698 JOHN G. KEMENY (Dartmouth College, Hanover, N. H.). **General Remarks on Markov Chains with Illustrated Examples in Biology.**

Part I of the paper deals with finite Markov chains. It is shown how, through intelligent classification of various types of chains and the use of modern matrix techniques, many fundamental problems can be reduced to routine computations. Two fundamental matrices are developed, one for absorbing and one for ergodic chains, in terms of which basic quantities can be simply expressed. As applications of these mathematical techniques, problems in genetics are considered.

Part II of the paper deals with some recent joint research carried on with J. L. Snell, concerning denumerable Markov chains. It is shown that extensions of the above-mentioned matrix techniques to denumerable chains result in an interesting discrete analogue of classical potential theory. While the discrete version is

simpler than the classical potential theory, it can be vastly generalized by extending it to a wide class of denumerable Markov chains. This has been done previously for transient chains, but the extension to recurrent chains is new. The fundamental matrices extend to basic potential operators. Applications of these results are sketched to population problems and to the spread of epidemics.

Throughout the paper, stress is laid on the methodological advantages of setting up a Markov chain model. A number of key results are stated without proof and several unsolved problems are mentioned.

699 OSCAR KEMPTHORNE (Iowa State University, Ames, Iowa), and R. N. CURNOW (University of Aberdeen, Aberdeen, Scotland). **The Partial Diallel Cross.**

The diallel cross, which is composed of all possible single crosses among a group of inbred lines, is a common plan of investigation in plant and animal breeding. It can be used to estimate general and specific combining abilities and variances, to estimate components of genotypic variation and to estimate yielding capacities of multi-way crosses. With n lines it does however involve $n(n-1)/2$ crosses, even if maternal effects can be ignored. Breeding programs can easily lead to 50 inbred lines which merit examination, so the diallel cross becomes unfeasible. This paper deals with sampling of the complete diallel cross table in a specific say, namely:

(1) arrange the lines in random order
(2) obtain the crosses of line i with lines

$$k+i, k+i+1, \cdots, k+i-1+s$$

where $k = (n+1-s)/2$ is an interger and all number above n are reduced by a multiple of n so as to be between 1 and n.

Each line is crossed then with s lines and $s = n-1$ corresponds to the complete diallel cross. This partial diallel cross is considered in the following respects:

(1) estimation of variance components
(2) comparing the yielding capacities of all possible crosses and
(3) estimation of general combining abilities.

The efficiency of the plan with regard to each of these aspects is evaluated and discussed. It is shown to be more efficient than some other possible plans under some circumstances.

700 BERTRAM S. KRAUS (University of Washington, Seattle, Wash.). **The Study of Human Growth: Some New Horizons.**

Researchers in biometrics, genetics, and physical anthropology have a fertile field for miscegenation in the study of growth. An example is the timely and significant problem of the possible genetic effects of irradiation on future human generations. Thus far workers in this field have failed to demonstrate that radiation causes mutations in the human species, although this can be assumed from experiments with other mammals. Perhaps this failure can be associated with insufficient knowledge or recognition of the nature of growth and the role of the genetic constitution in controlling or regulating growth. Perhaps, too, there has been too much emphasis placed upon clinical classifications of abnormalities (congential malformations) and not enough on the less dramatic but none the less real deviations in

patterns and rates of growth. Equally significant is the failure to define abnormality in terms of the statistical characteristics of the given population.

Attention is focused in this paper upon the distribution of certain skeletal phenomena in prenatal life—sequence of appearance of centers of ossification in the foot, changing long bone inter-relationships, and appearance of centers of calcification in the primary dentition. Norms for human populations are estimated for these traits. It is then suggested that significant deviations from norms established in control populations may reflect higher frequencies of mutant genes in a test population. A method is proposed for the study of the genetic effects of irradiation in Hiroshima and Nagasaki wherein the biometrist, the geneticist, and the physical anthropologist may pool their skills and concepts.

701 B. KURKJIAN (Diamond Ordnance Fuse Laboratory) and M. ZELEN (National Bureau of Standards, Washington, D. C.). **A General Theory for Analysis of Asymmetrical, Confounded Factorial Experiments.**

A general theory is developed for the analysis of factorial experiments involving an arbitrary number of factors and levels of each. The treatment-combinations are assumed to be assigned to an appropriate incomplete block design and the treatment estimates, t's, are computed in the usual way, ignoring the factorial correspondence between the treatments. New results are presented for obtaining the best linear estimates (and the associated var-cov matrix) of the various main effect and interaction parameters in terms of the t's. A condition on the var-cov matrix of treatment estimates, V_t, is provided which insures that the sum of squares of the various main effect and interaction terms is distributed as chi-square. Furthermore, a certain large class of partially balanced incomplete block (PHIB) designs with arbitary number of associate classes is described which can be treated by methods of this paper. The theory is applied to two PHIB designs involving three associate classes.

702 ROBERT S. LEDLEY (George Washington University, Washington, D. C.). **A Sequential Decision Theory Applied to Medical Diagnosis.**

The reasoning foundations of medical diagnosis involve two well-known mathematical disciplines; symbolic logic and probability theory. Value theory then can aid the choice of an optimum treatment.

Three factors are involved in the logical analysis: medical knowledge relating disease and symptom complexes; the symptom complex of the patient; and the disease complexes that are the final diagnosis. Each of these can be expressed as a Boolean function. The ease of making diagnostic tests varies greatly; a realistic method of diagnosis uses easier tests to select among more difficult tests.

Using probability theory, a 'most likely' diagnosis is determined by applying Bayes's formula to the conditional probability that a disease complex will produce a particular symptom complex and the total probability that any person chosen from the sample under consideration will have that disease complex. Certain problems arise in computing statistics for the probability determinations; the difficulty in obtaining 'sufficiently large' data and the time delay in gathering data.

Value concepts in medical diagnosis and treatment are concerned, for example, with decisions on whether to continue further testing, or what are the values of particular alternative treatment—diagnosis combinations. We distinguish three kinds of problems in treatment decision; under certainty, i.e. when the disease is

definitely known; under risk, i.e. when alternative diagnoses have been made with known probabilities; under uncertainty, i.e. when alternative diagnoses remain with no information concerning the probabilities.

703 **K. H. LU (Utah State University, Logan, Utah). The Means and Variances of the Products of Two or Three Normal Variables.**

Given normal variables t_1, t_2 and t_3 with means μ_1, μ_2 and μ_3, variances σ_{11}, σ_{22} and σ_{33} respectively. Let t_1 and t_2 follow the bivariate normal distribution with moment generating function:

$$M(t_1t_2) = \exp. \sum_{i=1}^{2} \mu_i t_i + \tfrac{1}{2} \sum_{i,j=1}^{2} \sigma_{ij}\mu_i\mu_j$$

Also let t_1, t_2, and t_3 follow the trivariate normal distribution with moment generating function:

$$M(t_1t_2t_3) = \exp. \sum_{i=1}^{3} \mu_i t_i + \tfrac{1}{2} \sum_{i,j=1}^{3} \sigma_{ij}\mu_i\mu_j$$

We define new variables x and y as follows:

$$x = t_1t_2, \quad \text{and} \quad y = t_1t_2t_3 \quad \text{respectively.}$$

It can be shown that by differentiating $M(t_1t_2)$ and $M(t_1t_2t_3)$ to obtain the appropriate partial derivatives evaluated at $t_i = 0$ and substituting into the definitions of means and variances, we have:

$$\mu_x = \mu_1\mu_2 + \sigma_{12},$$

$$\sigma_{xx} = \sigma_{11}\mu_2^2 + \sigma_{22}\mu_1^2 + 2\mu_1\mu_2\sigma_{12} + \sigma_{11}\sigma_{22}(1 + \rho_{12}^2),$$

$$\mu_y = \mu_1\mu_2\mu_3 + \mu_1\sigma_{23} + \mu_2\sigma_{13} + \mu_3\sigma_{12},$$

$$\begin{aligned}\sigma_{yy} = {} & \sigma_{11}\mu_2^2\mu_3^2 + \sigma_{22}\mu_1^2\mu_3^2 + \sigma_{33}\mu_1^2\mu_2^2 + \sigma_{11}\sigma_{22}\mu_3^2(1 + \rho_{12}^2) \\ & + \sigma_{11}\sigma_{33}\mu_2^2(1 + \rho_{13}^2) + \sigma_{22}\sigma_{33}\mu_1^2(1 + \rho_{23}^2) \\ & + \sigma_{11}\sigma_{22}\sigma_{33}(1 + 2\rho_{12}^2 + 2\rho_{13}^2 + 2\rho_{23}^2 + 8\rho_{12}\rho_{13}\rho_{23}) \\ & + 2(\sigma_{12}\mu_1\mu_2\mu_3^2 + \sigma_{13}\mu_1\mu^2\mu_3 + \sigma_{23}\mu_1^2\mu_2\mu_3) \\ & + \mu_1\mu_2(6\sigma_{23}\sigma_{13} + 4\sigma_{12}\sigma_{33}) + \mu_1\mu_3(6\sigma_{12}\sigma_{23} + 4\sigma_{13}\sigma_{22}) \\ & + \mu_2\mu_3(6\sigma_{12}\sigma_{13} + 4\sigma_{23}\sigma_{11}).\end{aligned}$$

704 **H. M. C. LUYKX and BETTY L. MURRAY (office of the Surgeon General U.S.A.F.). Durations of Illness.**

Using epidemiology in the broad sense of the word, one of the epidemiological characteristics of a disease is its duration pattern. Not only the mean duration will vary from one diagnostic entity to the next, but so will the shape of the distribution of durations, which can be described in several ways. In this paper a picture is presented for each of a number of specific diseases. For example, graphs are shown for 368 cases of infectious hepatitis, 446 cases of mumps, 879 cases of pilonidal

cyst and 2177 cases of streptococcal sore throat. These and other charts illustrate the techniques of analysis and presentation, and the use made of the data.

The curves are "cases—remaining" curves, which are strictly analogous to survivorship curves commonly given with life tables. A cohort begins its episode of illness at the zero point on a scale of days, and diminishes as each case terminates. The cases—remaining curves are more useful than ordinary frequency polygons (on a scale of duration). They show at a glance the range and skewness of the duration distribution, the modal day for return to duty, and the median and other percentile points on the "days-after-admission" scale.

The Air Force medical data are unique in that they provide unusually large frequencies, derived from uniform records and recording procedures, showing diagnoses established by a physician in each case. In this presentation, the beginning of an illness is excusal from duty by a physician, and the end is return to military duty; cases not returned to duty (deaths or disability separations from the service) are not included.

Definitions of illness, diagnostic entity, disability, admission, return to duty, etc., are also discussed, and a technical note describes the method of computing confidence intervals for percentile points.

705 CLIFFORD J. MALONEY (U. S. Army Chemical Corps, Ft. Dietrick, Md.). **Disease Severity Quantitation, II.**

It was previously shown (Disease Severity Quantitation. Paper read at Washington, D. C. 1959 Annual Meeting of the American Statistical Association) that symptoms of rats exposed to aerosol challenge of *B tularense* conform closely to a scaling model due to Guttman (Stouffer, S. A., Measurement and Prediction, 1950, Princeton U. Press).

Necessary and sufficient criteria of scalability are that symptom pairs yield four-fold contingency tables in which one, but not both, of the secondary diagonal cells are zero, and that the zero cells in all tables can be arranged in a linear order in either symptom designator.

The present paper points out that (in the absence of experimental accidents) the sum of the four cells in every table is fixed, that each table divides the entire disease severity scale into three intervals. In the first, the disease severity is too slight for either symptom to appear. In the second, the more sensitive symptom appears, but not the other, and in the last segment, the disease severity is such that both symptoms appear. The lower boundary is fixed by the milder symptom and is located at the same severity level whatever the other member of the pair; similarly for the upper level. Hence, a system of linear equations can be formed in the segment frequencies and in the segment lengths.

These sets can be equated and expressed in matrix notation. If the experimental data is perfect, the matrix will be triangular. If the data are subject to random error, the further treatment can be carried out in terms of a matrix subject to random error.

706 H. E. MCKEAN and B. B. BOHREN (Population Genetics Institute, Purdue University, Lafayette, Indiana. U. S. A.). **Numerical Aspects of the Regression of Parent on Offspring.**

The relative merits of three methods of estimating heritability from the regression of offspring on one parent's record, from the point of view of statistical

efficiency, are brought out with respect to five generations of a closed poultry flock previously reported by Yamada, Bohren, and Crittenden (*Poultry Science*, 1957). The three methods discussed are: (1) The regression of offspring means on parent records. (2) The regression of offspring records on parent records, in which the parents' record is repeated once for each progeny. (3) The Kempthorne—Tandon weighted technique (*Biometrics*, 1953), in which account is taken of the correlation coefficient ρ between errors associated with progeny of the same parent.

The latter technique (3) depends upon knowing ρ exactly; in this case the estimation technique is optimum. If ρ is unknown, ρ must be estimated or guessed; in which case (3) is not optimum. The loss in efficiency in misguessing ρ is discussed, over a range of possible values of ρ. A comparison is simultaneously made with methods (1) and (2).

The general conclusions, based on these data are: (i) method 1 is distinctly inferior to methods 2 and 3 in most conceivable situations; (ii) if ρ is small (which it is if the genetic variance is primarily additive and maternal effects are minor), then method (3) is only slightly more efficient than method (2). Indeed, method (2) is simply a special case of method (3) with ρ always guessed to be 0.

707 HARLEY B. MESSINGER (University of California, Berkeley, Cal.). **A Geometrical Model for Height-Weight Control Charts in Schoolchildren.**

The primary objective of this study was to obtain a satisfactory screening device, i.e., a way to give a yes-or-no answer at any time to the question, "Are this child's height and weight within the ranges one would expect knowing his age, sex, and previous heights and weights," To accomplish this, a set of tolerance limits were derived from the combination of cross-sectional studies of two functions of height and weight in one healthy group of children and longitudinal studies of these functions in each individual of a second healthy group with respect to the cross-sectional standards set by the first group. Because the functions were approximately independent, separate control charts could be used.

A secondary objective of the study was to seek interpretability for the control charts. In an interpretable chart, a child's ratings at any time can be related directly to his physical characteristics. A class of geometrically-meaningful functions arising from the use of a cylinder to approximate the human body was examined in the Institute of Child Welfare "Guidance Study" data. The height (H) of the cylinder and the diameter of the cylinder relative to the height (D/H) were essentially uncorrelated within each age group from 4 to 14 years. Individual children of the "Berkeley Growth Study" were studied longitudinally. Their H and D/Y functions at each age were studentized to obtain standard- or z-scores. From studies of these sequences as stationary autoregressive time series, reasonably efficient control charts were obtained. The D/H function, called "relative broadness," can be gotten from a nomogram. No arithmetic computations or standard-score tables are needed for this kind of chart.

708 CHARLES J. MODE (Montana State College, Bozeman, Mont.). **On The Theory of the Improvement of Metric Traits In Outbreeding Populations.**

An attempt was made in this paper to characterize the change in the mean and genetic variance of a metric trait under a program of improvement. The approach used in this paper differs from other approaches by carefully distinguishing

between the fitness of a genotype under a program of improvement and the metric trait. Only the single locus case with an arbitrary number of alleles was considered, but the model may be interpreted in such a way as to include the multi-locus case.

Steady state populations and the problem of stability of a steady state were also considered. The existence of steady states and the question of their stability was discussed for constant and non-constant measure of fitness.

The conditions for the existence of an optimal value for the mean of a metric trait when two or more alleles are maintained in a population under a program of improvement were also given.

709 W. S. OVERTON and A. L. FINKNER (North Carolina State College, Raleigh, N. C.). **The Sample Road-Block Method of Estimating Hunting Pressure.**

The sampling method described was developed for use on Game Management Areas in Florida, but is applicable in situations where estimates of hunting pressure are desired for areas having few or no inhabitants. The method involves the sampling of access points.

Under a given definition, it is possible to express "hunting pressure" in terms of total persons entering and leaving the area by time period. An expression is developed for the definition used in Florida, which forms the structural basis for sampling. Total hunting pressure is divided into a daily component and a component due to camping; only the former is considered in this paper.

The daily component of hunting pressure is a simple linear combination of the time period totals of entries and exits. There are a number of sampling systems that will give unbiased estimates of the totals by time periods, and, hence, unbiased estimates of the daily component. A system in which an observer measures a randomly selected station at alternate time periods with the starting time randomized among days was chosen because of its simplicity and ease of operation. Time periods are considered strata, and the usual stratified sample estimates of totals and variances are employed. This system does not yield unbiased estimates of variance, but seems to be satisfactory for present purposes.

Alternative sampling systems and corresponding estimates of variance are considered and evaluated.

710 D. S. ROBSON (Cornell University, Ithaca, N. Y.). **Cumulant component analysis in balanced designs.**

Cumulant components, as a direct extension of variance components, described the manner in which the usual assumptions on the linear model are violated. The unique, minimum variance unbaised estimators of cumulant components for the distribution-free, balanced model are easily determined because of the existence of a complete, sufficient order statistic. One computational procedure for constructing these estimates is an algebraic extension of the analysis of variance to the "analysis of cumulants".

Under the usual Model II assumptions of normality and independence of effects, the components of all cumulants beyond the second are zero. Tests of departure from zero, therefore, constitute tests of the usual assumptions. Several such tests are available.

711 B. V. SHAH (Iowa State University, Ames, Iowa). **Asymmetrical Factorials in Incomplete Blocks.**

The primary purpose of this paper is to summarize the recent developments in this subject and to indicate possible lines of attack for future research. After a brief summary on history of developments, the desirable properties of factorial experiments, namely orthogonality and balance are discussed. The analysis and the construction of the designs with above properties are studied. As a consequence of relaxing the condition on balance we obtain a wider class of designs, which may be called partially balanced factorial experiments. Finally, the use of pseudo-factors and some other aspects of these designs are studied.

712 R. G. D. STEEL (Cornell University, Ithaca, N. Y.). **A Variable Rank Sum Multiple Comparisons Test.**

A variable rank sum is used for the comparison of all pairs of treatments. This sequential method of testing should be more powerful than a procedure using a fixed rank sum and an experimentwise error rate. Computation of exact probabilities and appropriate tables is discussed.

713 PATRICK SUPPES (Stanford University, Stanford, Cal.). **Foundations of Measurement.**

This paper is concerned with the axiomatic foundations of measurement. The procedures and operations of measurement can be represented as a relation algebra in the sense of Tarski. The two formal theorems which demonstrate the adequacy of a particular scheme of measurement are the representation theorem which establishes that the algebra of empirical relations can be mapped homomorphically into the appropriate structure of the real numbers, and the uniqueness theorem which establishes that the homorphism is unique up to the appropriate group of transformations. Some empirical examples of these ideas are given and some problems of axiomatizability are mentioned.

714 WILLIAM F. TAYLOR (University of California, Berkeley, Cal.) and JOSEPH BERKSON (Mayo Clinic, Rochester, Minn.). **A Problem of Testing and Estimation Involving Four Fold Tables.**

In this paper, the old problem of the analysis of four fold tables is re-examined with respect to a peculiar kind of sampling. Assuming a population possesses properties A and B, consideration is given to several ways in which samples might be taken in order to determine whether A and B are associated.

Case 1. Simple random sampling. N members of the population are drawn at random and the frequencies of occurrence of A, B; A, not B; not A, B; and not A, not B are observed. This is the classical, simple sampling procedure.

Case 2. Sampling with respect to A. By this is meant the random and independent selection of N_1 members with property A and $N_2 = N - N_1$ members without property A. N_1 and N_2 are fixed in advance and the number of cases of B and not B are observed in each of these two groups.

Case 3 is the reverse of case 2, namely, sampling with respect to B.

In case 4, estimates of various parameters are found by one of Neyman's methods for obtaining best asymptotically normal estimates. A more recent method involving a logistic transformation is also used. The powers of several related χ^2 tests are

compared with the result that tests based on sampling by case 2 or 3 above have higher asymptotic power than one based on case 1 sampling. Case 4 lies between case 2 and case 3 in this regard.

715 ROBERT M. THORNER and QUENTIN R. REMEIN (U. S. Public Health Service). **Some Aspects of Screening Tests for the Detection of Disease Suspects.**

The screening of large population groups for chronic disease in a growing health department activity. The purpose of screening is the selection, for diagnostic evaluation, of persons in the population with a high probability of being diseased. The application of screening tests requires a basic knowledge of the attributes of these tests and an understanding of the results that may be anticipated when a particular test is applied to a population group at a selected screening level.

Tests used in screening must be simple and inexpensive; should be sensitive, specific, accurate, and precise. The theory of overlapping distributions is used to explain sensitivity and specificity. The stability of these measures and their relationship to prevalence is discussed. The effect of altered screening levels on sensitivity and specificity is illustrated.

Problems of selecting screening levels are discussed, together with the relationship of sensitivity, specificity and prevalence to the frequency of false negative and positive test results. Youden's test evaluation index is discussed in relation to comparing test results with chance.

The static and stochastic models of screening tests are considered, and "relative" sensitivity and specificity are reviewed. The calculation of confidence limits for sensitivity and specificity percentages is illustrated, and statistical techniques used for comparing results of different screening techniques, for correlated and uncorrelated models, are reviewed and illustrated. "Precision" and "accuracy" are defined, and the measurement of precision and comparison of precision measurements is illustrated.

716 R. M. THRALL (University of Michigan, Willow Run, Mich.). **A Review of Mathematical Aspects of the Theory of Measurement.**

The past fifteen years have witnessed a vast advance in the techniques and theories of measurement. Methods and theories appropriate to the physical sciences have been extensively generalized so as to become more applicable to the behavioral and life sciences. The present paper is limited to a review of certain mathematical systems which either have been used in measurement or show promise of such use.

Measurement in the physical sciences centered on description of some attribute of a physical object by a real number. S. S. Stevens pioneered in generalizing this concept of measurement, and his work stimulated still further generalization and abstraction.

A fundamental point of view in modern measurement theory is that the mathematical system used for measurement should be no stronger than is justified by the properties of the objects being measured. For example, use of the real numbers to measure hardness is not justified since neither addition nor multiplication has meaning relative to hardness. All that is physically meaningful is that relative to hardness objects can be placed in order with ties permitted. Thus for the "degrees of hardness" only a chain order is mathematically justified. The presence of ties in hardness indicates that a weak order is suitable for the objects themselves.

The present paper is devoted to a review of the development during the past fifteen years of mathematical models appropriate for measurement. These models vary in the strengths of the axiom systems used and in the extent to which stochastic theories are employed. Most of the early systems are entirely deterministic; later systems are increasingly stochastic in nature.

717 M. B. WILK and R. GNANADESIKAN (Bell Telephone Laboratories, Murray Hill, N. J.). **Some Remarks on Plotting Procedures in the Analysis of Experiments.**

The paper deals with certain problems of estimation, associated with plotting procedures in analyzing experiments, using rank order statistics. A detailed discussion of the half-normal plotting procedure in this connection is included.

The following are abstracts of papers presented at The Symposium on Quantitative Methods in Pharmacology held in Leyden, The Netherlands, May 10–13, 1960.

718 J. HAJNAL (London School of Economics, London, England). **Sequential Tests on Analgesics in Rheumatoid Arthritis.**

The paper is concerned with a series of clinical trials carried out in the Rheumatism Research Clinic of the Royal Infirmary, Manchester. The background and trial procedure are briefly described. The statistical analysis appropriate to this procedure, if sequential methods are not used, is compared with the sequential method in fact employed. The advantages and disadvantages of incorporating this sequential method in the design are discussed and some possible improvements in the sequential analysis are indicated.

719 N. L. JOHNSON (University College, London, England). **On the Choice of a Sequential Test Procedure.**

1. In the construction of a standard sequential probability ratio test (s.p.r.t.) procedure we need to define (i) two pivotal hypotheses H_0, H_1, (ii) two (approximate) probabilities of error α_0, α_1, such that

$$\Pr\{\text{reject } H_j \mid H_j\} \cong \alpha_j \qquad (j = 1, 2).$$

It is known that the s.p.r.t. is then optimal in the sense that among all procedures satisfying (ii) the s.p.r.t. has (nearly) the smallest expected size of sample whether either H_0 or H_1 is true.

2. Conditions (i) and (ii) are the same as those often used in determining the size of sample to be taken in a classical fixed sample procedure. In such cases the hypotheses H_0 and H_1 (and the probabilities α_0 and α_1) are chosen in the light of the required sensitivity of the procedure. For example H_0 may be a 'null hypothesis' (and α_0 a 'level of significance') corresponding to a desirable level of quality, with H_1 representing a change in quality of such an amount that a high probability $(1-\alpha_1)$ of detecting it is needed.

If H_0 and H_1, determined in this way, are used to define a s.p.r.t., the full advantage of the sequential method may be lost unless either H_0 or H_1 is true (or nearly so) in a large proportion of cases. When a hypothesis H, different from both H_0 and H_1, is true there is no guarantee that the s.p.r.t. procedure defined by H_0, H_1, α_0, α_1 will even have a lower average sample size than a fixed sample procedure defined in the same way.

3. A s.p.r.t. satisfying (ii) need not necessarily be based on H_0 and H_1 as pivotal hypothesis. It is suggested that consideration should be given to the introduction of additional hypotheses H_0' , H_1' , to be used as pivotal hypotheses. H_0' and H_1' would be chosen to represent the sort of conditions expected to be encountered rather frequently—so that the saving in average sample size should be as effective as possible. The associated (approximate) probabilities of error α_0' , α_1' (where Pr {reject H_j'/H_j'} $\cong \alpha_j'$; $j = 1, 2$) are then determined by conditions (ii).

4. In this paper detailed consideration is given to the case when the s.p.r.t. is regarded as a test of the 'null hypothesis' H_0 , and where we take $H_j' = H_0$. Some tables are given to aid in the construction of the test procedures, and also to describe the properties of such tests.

5. Incidentally to the main topics, some results are obtained on the conparison of operating characteristics (or power functions) of comparable s.p.r.t.'s.

720 CHR. L. RÜMKE (Free University of Amsterdam, Neth.). **An Efficient Design for Comparing the Effects of Two Treatments.**

The variability of the reactions of groups of animals to drugs often interferes with an efficient comparison of the effects of two treatments with all or none responses. In classical ED_{50}-determinations it is difficult to choose such dose-levels that the inefficient 0- or 100% effects are avoided. A design is to be described which leads to an efficient test for the difference between two treatments at an optimal dose level. A rough estimate of the ED_{50}'s can be made by slightly modifying this design—though with some loss of efficiency.

721 K. L. SMITH (Boots Pure Drugs, Nottingham, England). **Sequential Analysis Applied to Biological Control Tests for Pharmacopoeial Substances.**

During some biological examinations to control the quality of pharmacopoeial substances, sufficient evidence may be obtained at one time to satisfy the official requirements and the results from such examinations may be analysed by the traditional methods.

In some examinations, such as those to exclude undue amounts of pyrogens, the evidence collected at one time may be sufficient to accept or reject the material in the extreme cases. For intermediate cases repeat tests are permitted and the criteria for them may be conveniently derived from a sequential sampling plan.

In a large number of tests the evidence must be collected sequentially either as single responses as in the assay of Digitalis using guinea pigs or pigeons, or as the results from repeated tests which individually are too imprecise as in the assay of Insulin. Both circumstances lend themselves to the application of sequential analysis. In both cases where one has set out to make a certain number of observations before applying traditional methods of analysis, the value of using a sequential plan may be one of economy only. In those cases where testing is continued until the sample may be considered satisfactory, it is essential that the amount of repeat testing should be sufficient to satisfy a sequential sampling plan.

722 D. J. MÊWISSEN and E. H. BETZ (l'Universit. de Liège, Belgium). **Sequential Tests in Protective Effects of Cystamine and Chlorpromazine.**

A simple method based on sequential test has been used by KIMBALL and al. (Radiation Research, 7, 1, 1957) for screening compounds in radiation protection.

Under specific conditions, the method is easy to apply and the decision of accepting or rejecting a prospective action of protection is based on the difference in animals surviving in the treated and control groups.

The effectiveness of protective agents widely varies with the delay between administration to animals and exposure. The responsible factors and the underlying mechanisms are poorly understood. Therefore, we investigated variations in the protective action of cystamine and chlorpromazine versus delay in X-irradiation of treated animals. Usual sampling methods would have been unpractical and expensive as existence of a protective effect was questionned under various time specifications. Sequential tests were used. A 60% survival in the treated group was assumed a meaningful increase over 50% survival in the control group. Maximum risks for both kinds of errors were set at 10%. Tests were arbitrarily stopped after five steps. Decision was usually reached after three steps.

In a first series of experiments, groups of ten animals were used. In treatment groups, chlorpromazine (5 mg) was injected intraperitoneally to adult pure inbred rats (average body weight: 180 g), respectively 2, 3 and 4 hours prior to total body irradiation (750 r). In a second series of experiments, groups of 5 animals were used. Cystamine (100 mg/100 g of body weight) was injected intraperitoneally to rats, respectively 2, 10, 20, 30 and 45 minutes prior to irradiation (900 r). In each instance, a sequential test was performed on successive groups. In addition, mortality in all groups was recorded for 30 days and mortality curves were drawn. In all cases, decisions reached at an earlier stage with sequential tests were confirmed by further examination of the completed mortality curves.

723 E. W. PELIKAN (Boston University, Boston, Mass., U. S. A.). **Dose Metameters in Comparative Pharmacology.**

Both inter-species and intra-species comparisons of sensitivity to drugs of common mammals, including man, may be facilitated by expressing dose as a power function of body weight. Determination, from published data, of the constants in the equation [log mean total dose (mg) = b log mean body weight (gm) + a] yielded the power function best suited to inter-specific comparison of potency of drugs of three classes. When paralysis was the criterion of effect, b for tubocurarine, its dimethylether, benzoquinonium, gallamine, and succinylcholine did not differ significantly from 1.0; for decamethonium, b was 0.60, significantly less than 1.0. When anesthesia was the effect, b for amobarbital, pentobarbital and secobarbital was about 0.80 and b was independent of route of parenteral drug administration. When acute death was the effect, b was 0.83 for ouabain, 1.01 for digitalis tincture. In contrast, analogous values of b for digitoxin, digitalis, ouabain or Lanatoside C (computed using data for total lethal doses and body weights of individual members of a given species) varied from 0.52 to 0.89 (median: 0.70) for these drugs in each of several species. Minimizing inter-species variance in potencies of drugs, precision in estimating and predicting drug potencies among species or individuals, and detection of species differences in sensitivity to drugs may be furthered by use of an appropriate dose metameter.

724 P. J. CLARINGBOLD and C. W. EMMENS (University of Sydney, Australia). **Biological Assays Involving Quantal and Semi-quantal Responses.**

Various transforms have been used for interpreting the results of biological assays and other experiments when the response is quantal. Usually, intervals

are studied in which transforms such as the probit, logit or angular show no perceptible differences, and it is a matter of practical convenience which is used. The angular transform is often the most useful, as it has equal weights at all response levels.

In much early work, few dose-response lines had to be calculated, and the design of tests was simple. More and more frequently however, screening trials or complex designs require methods which offer rapid analysis, even if approximate. Also, within-animal quantal assay will usually yield few responses from each animal and the application of even the angular transform becomes extremely complex. In such circumstances, analyses of variance of the untransformed data (scored 0, 1 or 0, 1, $\cdots$ n) is defensible and gives rapidly computed estimates which show little loss of information and allowed of up to a 4-fold increase in precision in cross-over assays with mice. In factorial tests, probit or even angular transformation leads to formidable computations if many factors are involved, whereas analysis of variance of the untransformed data is simple and remarkably accurate in practice.

725 R. VAN STRIK (Philips-Duphar, Weesp, Neth.). **A Simple Method of Estimating Relative Potency and its Precision from Semi-quantitative Responses.**

A simple procedure is described for evaluating those bio-assay experiments where the observed responses are scored in a semi-quantitative scale, such as $=$, $+$, $++$, $+++$. The initial responses are ranked together in order of magnitude and a potency ratio with its confidence limits are calculated from the ranks using customary bio-assay computational methods with just one minor alteration. The method is outlined in an example and its reliability is investigated.

726 CLAUS RERUP (The Royal University, Lund, Sweden). **On the Validity of a Cross-over Assay.**

Cross-over assays are valid only, when the following criteria are fulfilled:

1) The assay design has to be balanced, which means that a set of observations always has to be obtained not only in a certain order, but simultaneously in the reverse order because of possible changes in the magnitude of reactions between treatments within subjects.

2) No significantly different changes in reaction between groups of subjects are allowed to occur from treatment to treatment.

For the twin and triplet-cross-over assay (insulin, corticotrophin) it is shown that the hitherto applied validity tests (in the twin cross-over assay the test for parallelism of the dosage response lines for standard and test, in the triplet cross-over assay extended by a test for curvature of the mentioned lines) are not appropriate, because group differences may cause apparent significant differences in slope. Group differences are, however, eliminated in the cross-over analysis. An example of a twin cross-over assay on insulin is given, which must be regarded as invalid according to hitherto published validity criteria, which, however, is a good and valid assay according to the essential validity criteria to be presented in the paper.

727 J. HEMELRIJK (Technological Institute, Delft, Neth.). **Experimental Comparison of Student's and Wilcoxon's Two Sample Tests.**

The choice between the many available statistical methods is often difficult to make in practical situations. It is often—too often—based on personal preference

without sufficient regard for the merits of the different methods available. A lack of knowledge about the small sample properties of many distribution-free methods tends to make their position uncertain in comparison to classical methods, based on specified suppositions about the sampled populations; the properties of the latter are known, if these suppositions are true.

In a small experiment, using QUENOUILLE's (Biometrika, 46 (1959), 178—204) 50 independent pairs of samples of size 10 were used to compare STUDENT's and WILCOXON's two sample tests.

The samples were first taken from a standard normal distribution (QUENOUILLE's $_1$), then one of them was shifted over distances of 0.81; 1.05 and 1.53 to the right. These shifts correspond to a power for STUDENT's test of 0.40; 0.60 and 0.90 respectively. In all these positions both tests were applied onesidedly with level of significance 0.025. As was to be expected—STUDENT's test being uniformly most powerful in this situation—the power of WILCOXON's test was the smaller one. The results indicated that in this case one would not be far off the mark in stating that, roughly, the loss of power was about 10% of the power of STUDENT's test as long as the latter is not too close to 1. (This also holds under the hypothesis tested: the true level of significance is for STUDENT's test 0.025 and for WILCOXON's test, owing to its discrete character, 0.022 in this case.)

A second point of investigation was the reaction of the tests to an observational error in one of the original observations. For each pair of samples an observation was chosen at random from the sample with the larger median and this observation was shifted over a distance 2 to the right. In accordance with expectation STUDENT's test proved to be far more sensitive to this mild kind of slippage than WILCOXON's test.

Finally all observations, transformed to observations from a rather skew exponential distribution (QUENOUILLE's χ_4), were again tested in the same way. The shifts were in this case replaced by multiplication of the observations of one of the samples from the starting point of the distribution, in order to keep this point invariant. The factors were: 1 (identical distributions); 2; 3 and 4.5, resulting in power function values of roughly 0.025 (the level of significance); 0.25; 0.45 and 0.70 respectively. The two tests were now approximately equally powerful.

All these results are dependent in a statistical sense, being based on the same 1000 observations. Also the investigation was too small (although laborious) to warrant strong conclusions. It is only the beginning of more extensive research with more powerful means.

H. DE JONGE (Netherlands Institute of Preventive Medicine, Leyden, Neth.).

728 **The Influence of Non-normality on the Significance Levels of Student's Two Sample Test.**

The paper describes an empirical sampling study of the distribution of Student's t for small samples taken from four populations with non-normal distributions, respectively showing: A. Marked skewness, B. Skewness with a bunch of outliers, C. Leptokurtosis with skewness, D. Platykurtosis with skewness. These types of distributions were chosen, because they were frequently seen in practice.

From each population pairs of random samples of 5, 10 and 20 elements were drawn and the values of t were computed. For each of the populations and for each sample size the empirical sampling distribution of t has been compared with the corresponding Student-distribution.

729 H. R. VAN DER VAART (University of Leyden, Neth.). **On the Robustness of Wilcoxon's Two Sample Test.**

It has long been known that the probability of Type I error of Student's two sample test is subject to appreciable variation in the case of unequal population variances (Hsu, 1938, Stat. Res. Memoirs; Chand, 1950, Ann. Math. Stat.). Therefore it is interesting to know the behaviour of Wilcoxon's two sample test in this respect. Van der Vaart (1950), Indag. Math.) found in a special case for very small samples that Wilcoxon's test is less sensitive to inequality of population variances than is Student's tests, Kruskal and Wallis (1952, Journ. Amer. Stat. Assoc.) put forward an argument which lends plausibility to the conjecture that Wilcoxon's test may be fairly insensitive to differences in variability, and Hodges and Lehmann (1956, Ann. Math. Stat. p. 327–329) show that Wilcoxon's test is often less powerful against contamination with a shift than is Student's test. All this might lead one to expect that Wilcoxon's test would in general be less sensitive to the above-mentioned inequality of variances than is Student's test. Now this turns out not to be uniformly true. For instance, in the extreme case where one of the population variances is zero, the relation between the sample sizes determines which test will behave worst in this respect. In the general case the situation is rather complicated.

730 I. JUVANCZ (Math. Institute, Hungarian Academy of Science, Budapest, Hungary). **Contra Indication of Non-parametric Tests in Medical Experimentation.**

According to the author's personal experience from the design and/or analysis of over 700 experiments (most of them medical), the statisticians engaged in medical experiments show a reluctance to use non-parametric methods, though numerical theorists enthusiastically advocate them. A statistical survey is made of papers from some medical, biometrical and statistical periodicals, published in various countries. The results show the same tendency as the author has noted at home.

The reluctance of those "qualified in medicine or, if not so qualified, at least well soaked in it" is caused by some characteristic features of medical experimentation, well known to them. So e.g. in medical experiments the interest is mainly centered on the estimation of mean values and their fiducial limits and on material significance. There is great variation between and within individuals; the measurements are poor; the number of observations is small. Experiments are sometimes dangerous. Numerous factors disregarded in the statistical analysis influence the final decision. Experimental results are retested several times by others before they are accepted. The results are often intended for individual use (e.g. diagnostic test). Etc. etc.

These characteristics compel the researchers to use statistical methods which yield results convertible to the original measure (e.g. kg, cm). Order statistics and the χ^2-tests are not of this kind. Further, to minimize the loss of information non-parametric methods are too wasteful. Consequently non-parametric tests are economically inefficient both qualitatively and quantitatively.

Not rarely are non-parametric tests insensitive to changes regarded medically substantial and too sensitive to insubstantial ones. (E.g. χ^2-tests are insensitive to consistent though little increasements and sensitive to great though inconsistent ones; this is not the case with the t-test.) If is often impossible to decide what caused the statistically significant change indicated by a non-parametric test (mean,

type of distribution etc.). On the other hand, tests of the mean are very "robust" against non-normality.

Only a small field of application is left for non-parametric methods: the cases where the experimental techniques are too weak; e.g. when the results are only given in rank-numbers as sometimes in psychometrics.

Consequently, the use of non-parametric methods should be avoided, if necessary by the invention of better experimental (e.g. chemical) methods.

731 L. J. GOLDBERG (University of California, Berkeley, Cal., U. S. A.). **A Visual Statistical Approach to Bio-assay.**

In quantal bio-assay one usually starts with the following information:

'A series of doses $(d_1, d_2, \cdots, d_i)$ has been administered to $(N_1, N_2, \cdots, N_i)$ test hosts respectively, and the corresponding reactors $(r_1, r_2, \cdots, r_i)$ are observed at each test dose level'.

Based on a set of such experimental observations, a visual procedure will be presented for estimating the true dose response. The proposed procedure is based on the concept that a single experimental observation should be considered as a triplet (r, N, d). The entire set of experimental observations may be considered as follows, in triplet notation.

$$(r_1, N_1, d_1), (r_2, N_2, d_2), \cdots, (r_i, N_i, d_i).$$

The problem of estimation is reduced to the operation of 'triplet addition' conditional to an assumed dose response model. The rules for triplet addition will be illustrated in detail for the single hit dose response model. The extension to other dose response models will be considered, including the logit and probit as specific examples.

732 CONSTANCE VAN EEDEN (Mathematical Centre, Amsterdam, Neth.). **On Distributionfree Bio-assay.**

In bio-assay the following situation is considered: a stimulus (e.g. a drug or a vitamin) is applied to a subject, resulting in a response produced by the subject. In this paper we only consider the quantal (all-or-nothing) response. Then for each subject there will be a level of intensity of the stimulus above which the response occurs and below which it does not occur; this level is called the tolerance of the subject. On a population of subjects this tolerance will be a random variable λ, with distribution function $F(\lambda)$, say. The problem in bio-assay is to give an estimate of this distribution function $F(\lambda)$. A second problem is to compare the distribution functions $F_1(\lambda)$ and $F_2(\lambda)$ for two different stimuli. The observations then consist of the results of applying the stimulus once to each of a number of subjects, at several doses.

The abovementioned problems are solved for the parametric case, e.g. when λ has a normal distribution; the methods given for this situation are called "probit analysis" and are described e.g. by D. J. FINNEY (1947).

The application of this method, however, requires in some cases laborious computational work. Moreover difficulties arise if, for one or more doses the number of observations is very small or if none of the subjects or all subjects give a response. Finally the assumption of normality may not be fullfilled.

This paper contains a description of what may be obtained if no assumptions are made on the form of the distribution of λ. Let observations be available at

k different doses $d_1, \cdots, d_k$ with $d_1 < \cdots < d_k$. The number of observations at dose d_i is denoted by n_i and the number of subjects giving a response at dose d_i is denoted by a_i. We suppose all observations to be independent. Let further p_i denote the probability that a subject gives a response at dose d_i then $p_i = F(d_i)$; consequently, $F(\lambda)$ being a monotone non-decreasing function of λ, we have $p_1 \leqq \cdots \leqq p_k$.

For this situation maximum likelihood estimates of $p_i = F(d_i)$ may be obtained by means of a method described in the thesis of C. VAN EEDEN (1958). In this thesis a more general problem is considered, where k parameters of k distribution-functions are to be estimated, if it is known that these parameters are partially or completely ordered and moreover confined to given intervals I_i. If the distributions are binomial, the ordering is complete and I_i is the interval [0, 1], we obtain the above mentioned problem of estimating probabilities $p_1, \cdots, p_k$ satisfying $p_1 \leqq \cdots \leqq p_k$.

These maximum likelihood estimates may be obtained in a simple way and it is not necessary to have a large number of observations at each dose. Thus a maximum likelihood estimate of $F(\lambda)$, at the doses used in the experiment, is obtained without any assumptions of a parametric nature about the distribution function $F(\lambda)$.

References

VAN EEDEN, C. (1958), Testing and estimating ordered parameters of probability distributions, Thesis Amsterdam.

FINNEY, D. J. (1947), Probit Analysis, Cambridge University Press, Cambridge.

733 C. W. DUNNETT (University of Aberdeen, Scotland). **Statistical Theory of Drug Screening.**

Screening a chemical compound for some specific form of chemotherapeutic activity is considered as a decision problem in which the terminal decisions open to the investigator are either to accept the compound as being worthy of further investigation or to reject it as being of no interest and the unknown "state of nature" is the degree of activity of the compound. A truncated sequential procedure for screening is proposed, in which rejection can occur at any stage but acceptance is allowed only at the final stage. The particular case in which only two levels of activity exist (called "active" and "inactive") and all compounds have the same *a priori* probability of being active is considered in detail. A criterion of optimality is introduced, which involves the cost of testing and the costs associated with wrong decisions. A method for computing the critical rejection levels when the testing errors are normally distributed is given, and illustrated for one, two and three-stage procedures. Extensions to cases in which some compounds are more likely to be active than others, and in which more than two levels of activity may occur, are discussed.

734 M. A. SCHNEIDERMAN (Cancer Research Institute, Bethesda, Md., U.S.A.). **Statistical Problems in the Search for Anti-cancer Drugs by the National Cancer Institute of the United States.**

The development of the external (contract) screening program of the Cancer Chemotherapy National Service Center is described. The basic experiment is a

joint toxicity-therapeutic trial. This permits the administration of maximum tolerated doses without the need for extensive prior toxicity testing. The basic screen uses three different mouse tumors with each tumor system examined independently. A multi-stage sequential scheme is exployed; a two-stage scheme for "natural" products and a three stage scheme for synthetic chemicals. The operating characteristic curves for the two systems are compared. The acceptance and rejection levels have been so adjusted that the two systems yield the same number of false positives, while the two-stage scheme yields more false negatives. This can be tolerated because of the nature of the natural products coming to the screen. The actual behavior of one of the screens is appraised by examining the responses to a "known positive" compound, tested by different screeners in different places at different times.

Problems of mechanical data processing, the use of additional screens beyond the basic three, secondary screening, optimal dose-finding, "positive" and "negative" controls, possible deterioration of natural products, and some possible nonparametric approaches are considered, as examples of unsolved problems.

735 J. J. GRIMSHAW and P. F. D'ARCY (Allen Hanburys, Ltd., Ware, England). **Some Problems Arising in Drug Standardization and the Selective Screening of Compounds of Potential Pharmacological Interest.**

During the course of routine standardization and screening procedures a variety of problems have been encountered. Examples of *in vivo* and *in vitro* techniques are given, in which the assays of purgatives and succinylcholine together with the screening of potential analeptics and barbiturate potentiating drugs, antihistamines and neuromuscular blocking agents are considered. Solutions to some of the problems are proposed and the need for careful statistical control throughout is emphasised. It is suggested that, in some cases, insistence on statistical rigour may lead to results of diminishing practical importance, and the implications of this are discussed.

736 NORBERT BROCK (Asta Werke, Brackwede, Germany) and BERTHOLD SCHNEIDER (Karlsruche, Germany). **Pharmacological Characterization of Drugs by Means of the Therapeutic Index.**

For the pharmacological characterization of drugs it is not sufficient to describe their different qualities of action as such; in order to obtain a clear picture of the value and dangers of any substance, i.e. of its margin of safety, it is necessary to plot one of its actions against the other. As a measure of the margin of safety we introduced the therapeutic index (*DL* 5/*DC* 95 or *DL* 5/*DE* 95) which expresses the relation between the curative and toxic doses. Based on more than 10 years' experience, the author discusses some practical examples in various fields of pharmacotherapy. The trouble in applying the therapeutic index is the difficulty in obtaining approximate values for the deviations of the index and in having suitable testing methods available. Both problems are discussed and suggestions made for practical use.

737 E. J. ARIËNS (University of Nijmegen, Neth.). **Analysis of the Action of Drugs and Drug Combinations.**

As a rule the determination of biological activities of drugs aims at the comparison of the results obtained with various drugs or with one drug under different

circumstances, as for instance different doses. The experiments must therefore be based on a sound design and the experimental results evaluated with the aid of statistical methods. A primary question remains, however, whether the effects or magnitudes that are compared are really comparable in the sense meant by the investigator. This is especially of importance if the experimental results serve the study of relations between the chemical structure of drugs and their biological activity. Based on the result of such studies a more direct design of new drugs, with a minimum of trial and error in the research procedure, might be possible. If experimental data are compared, an analysis of the biological effects studied is necessary in order to find out if, to what degree and in what sense these data are comparable. This will be demonstrated by some examples.

738 S. DIKSTEIN (Hadassah Medical School, Jerusalem, Israel). **Physical Chemistry of Drug-receptor Interaction.**

1) The effectivity in vitro of homologous series of aliphatic choline esters, straight chain aliphatic primary amines and straight chain aliphatic monoquaternary ammonium compounds was determined on the small intestine of guinea pig.

2) Morphine, an inhibitor of the acetylcholine release, inhibits the contractions caused by small doses of nicotine, but has no effect on the contraction caused by acetylcholine. This phenomena is similar to the inhibition caused by botulinum toxin, which is known to act at the nerve ending. Since morphine has no effect on the contractions caused by any of the homologous amines tested by us, it was concluded that the primary amines and monoquaternary ammonium ions act directly on the smooth muscle.

3) In the homologous series, the activity increases with increasing number of methylene groups up to a certain limit, the further addition of a single methylene group then abolishes the contractive power or makes the compound inhibitory. Addition of more methylene groups first increases the inhibitory power and then decreases it.

4) A qualitative explanation is offered to explain the observed facts. According to this hypothesis in the presence of a positive charge, if the solubility parameter of the compound is higher than that of the biophase we get excitation, if the solubility parameter is lower we obtain inhibition. The smaller the difference the greater the effectivity. On the molecular level the excitation is explained by other workers by the interaction of materials with monolayers. According to this work it is postulated that if the material has a lower solubility parameter than that of the biophase it will dissolve in it increasing the spreading force. A material with higher solubility parameter will decrease the spreading force.

5) Since the excitation is a kinetic phenomenon (the velocity of addition of the excitant determines the activity) whereas the solubility parameter represent in fact a term of energy, it is not difficult to explain the absence of quantitative predictions.

6) The importance of the solubility parameter in other drugs is discussed.

739 S. E. DE JONG (University of Leyden, Neth.). **Isoboles.**

In this lecture reference is made to Loewe's method, by which the pharmacological effect of two drugs in combination is diagrammatically represented by means of isoboles.

A definition with a short description is given, followed by a survey of the most

important types. Some special cases are discussed more fully. It is explained that some forms of synergism do not lend themselves to being represented by means of isoboles (allobiotic synergism; inversion). Not only because of this do the isoboles not yield an optimal solution to the pertaining problem. It may be considered objectionable that it is necessary to estimate the exact amounts of a series of mixtures of two drugs needed for a quantitatively specified effect. Besides, the isobole thus obtained even then gives only incomplete information; for stronger or weaker effects an entirely different type of isobole can be found.

In conclusion Loewe's rather complicated nomenclature is enumerated.

740 P. S. HEWLETT and R. L. PLACKETT (Pest Infestation Laboratory, Slough, England). **Models for Quantal Responses to Mixtures of Two Drugs.**

The various previous approaches to the construction of mathematical models for quantal responses to mixtures of drugs are briefly referred to, and it is pointed out that models for graded responses to mixtures cannot in general be transferred direct to the interpretation of quantal responses. A general method for developing models for quantal responses to mixtures is put forward. This is exemplified by development of a model for simple similar joint action, i.e. a situation in which two drugs have a common site of action, but in which neither modifies the behaviour of the other at their site of action or elsewhere.

741 J. GURLAND (Iowa State University, Ames, Iowa, U. S. A.). **Determination of Minute Insecticidal Residues through Biological Assay.**

Samples of alfalfa from a field sprayed uniformly with Guthion, were collected 1 day, 3 days, 7 days, 2 weeks, 4 weeks after spraying. The residue in these samples was determined by means of a biological assay in which houseflies were exposed to increasing doses of the insecticide. Since sample extracts contained lipids and other materials which caused a masking effect, the standard preparations used for comparison were made to contain comparable amounts of control extract. The usual type of parallel line assays employing mortality of houseflies were employed for determining the residues in the 1-day, 3-day, and 7-day samples, but the extracts for the later samples had to be fortified with known amounts of the Standard in order to raise the response from a very low level to a level at which a parallel line assay could again be employed.

To increase the sensitivity of the technique it was found that the ratio of the volume containing the fortifying Standard to the volume of the Test extract should be made as small as possible. Further, the final volume of Test extract should be small relative to the sample mass being extracted in order to increase the sensitivity expressed in such units as parts per million of sprayed alfalfa.

742 A. G. MATHEWS (Dept. of Health, Victoria, Australia). **The Interpretation of Antibiotic Blood Level Curves.**

Although hundreds of investigations of antibiotic blood levels have been reported, in comparatively few has any examination of the statistical significance of observed differences been performed, and in even fewer has any attempt been made to assess the pharmacological significance of the results. Consequently, the literature is filled with conflicting reports as to the relative efficacy of various dosage forms,

and the lack of adherence to any common experimental design makes the resolution of such conflicts very difficult.

The problem of deriving a single statistic, with which to summarize the information contained in a set of blood level curves, is rendered difficult through ignorance of the relative importance of the height of the peak, the time at which the peak occurs, and the period during which the curve is above an arbitrarily chosen level. Attempts which have been made to derive such statistics will be reviewed, and their limitations discussed.

The shape of the blood level curve in the region of the peak is usually difficult to determine, because of practical objections to the frequent collection of samples of blood. Advantages of experimental designs, in which only a few samples are required from each of many subjects, will be discussed.

No matter how carefully sets of blood level curves may be determined, nor how ingeniously their properties may be summarized statistically, the problem of pharmacological interpretation remains. Stress will be laid on the importance of ancillary studies: for example, of the rate of excretion of the antibiotic, and of its distribution in the tissues of the body.

743 W. Z. BILLEWICZ (University of Aberdeen, Scotland). **A Statistical Investigation of Factors Affecting the Accuracy of D_2O Determinations by the Falling Drop Method.**

After a short description of the method the results of the analysis of the trial series are briefly discussed and taken as the basis of subsequent experiments. The experimental results cover various aspects of the method. The effects of changes in room temperature, position of the dropping tube and dropping technique are considered. Errors of the distillation stage are considered and discounted. The problem of the optimal selection of tube and drop size is considered in some detail in terms of an index of sensitivity of the method. Errors resulting from observer timing as opposed to photo-electric timing are discussed. A comparison of two main estimation methods is made and finally the problem of serial estimates on the same subject is considered.

744 J. DUFRENOY (Conservatoire National des Arts et Métiers, Paris, France). **Using the Arc Tangent Scale for Quantitative Methods.**

The arc tangent scale, used either for the abscissa or the ordinate scale, or for both, is most convenient for plotting "responses" as the dependant variable, ... the range 0 to 100, against the independant variable, in the range 0 to infin...

The arc tangent is most eminently suited for transformation of the time ... into a metameter (τ).

THE BIOMETRIC SOCIETY

British Region

The following Officers have been elected for 1961:

President: J. A. Fraser Roberts
Secretary: C. D. Kemp
Treasurer: P. A. Young.

The Summer Meeting of the Region was held on July 6, 1960, at the National Vegetable Research Station, Wellesbourne, Warwick.

A meeting on October 27, 1960, was concerned with "Applications of Electronic Computers to Biological Problems." The following papers were read and discussed:

W. T. Williams—Some Applications of Electronic Computers in Plant Ecology and Taxonomy.
J. N. R. Jeffers—Data Processing in Biological Research.
F. Yates—Problems Arising in the Use of Electronic Computers in Statistical Analysis.

Following the Annual General Meeting on December 13, 1960, the following papers were read and discussed:

C. W. Emmens—The Planning and Analysis of Some Field Trials with Cattle.
C. C. Spicer—Problems in the Analysis of a Large Scale Clinicial Trial.

On January 2, 1961, a special meeting was held on "Biometrical Aspects of Plant Growth" in collaboration with the Society for Experimental Biology. The programme included:

J. A. Nelder—Models and Experiments for Growth Analysis
S. C. Pearce and C. S. Moore—A Study of the Sources of Variation in Growth of Fruit Trees.
M. J. R. Healy—Experiments for Comparing Growth Curves.

A general discussion was led by F. L. Milthorpe.

E.N.A.R.

The following officers have been elected for 1961 by the Eastern North American Region:

President, 1961: Oscar Kempthorne
President-elect, 1961: Henry L. Lucas
Secretary, 1961: Erwin L. LeClerg
Treasurer, 1961: Donald A. Gardiner
Regional Committee, 1961–63: Virgil L. Anderson and Robert J. Monroe.

ENAR TREASURER'S REPORT FOR 1960

Marvin A. Kastenbaum, *Secretary-Treasurer*

INCOME

Balance Forward		
Checkbook balance Dec. 31, 1959		$ 324.29
Dues payments		5,181.50
Share of Proceeds from Washington meeting (1959)		267.88
Credit on Canadian checks		.40
Payment from WNAR for Programs		5.00
Sustaining member credit		100.00
Payment from AIBS for printing		14.00
		$5,893.07

EXPENSES

Checks not honored		$ 14.00
Refund on dues		.50
Treasurer International		4,465.00
Transfer to Savings Account		267.88
ENAR expenses		
Postage	$187.93	
Printing	365.78	
Clerical	30.96	584.67
Checkbook Balance December 31, 1960		561.02
		$5,893.07

OPERATING ANALYSIS

Operating income		
Dues payments	$702.00	
Other societies	19.00	
Bank credit on checks	.40	
Sustaining member credit	100.00	$ 821.40
Operating expense		584.67
Surplus for 1960		$ 236.73

CHECKBOOK BALANCE

Advanced from 1959	324.29	
Surplus for 1960	236.73	
Checkbook balance November 15, 1960		$ 561.02

SAVINGS ACCOUNT BALANCE

Advanced from 1959	716.11	
Interest 1959	6.26	
Proceeds from Washington meeting (1959)	267.88	990.25
Total cash in Bank December 31, 1960		$1,551.27

W.N.A.R.

MINUTES OF THE WNAR BUSINESS MEETING

The annual meeting of the Western North American Region of the Biometric Society was held at 1:00 P.M., August 24, 1960, on the Stanford University Campus. William Taylor, President, WNAR, presided. The highlights of the minutes of the previous meeting were read by the Secretary, Walter Becker, and were approved. The Secretary then gave his report. A method for obtaining News and Announcement for *Biometrics* was described. This consisted of sending to everyone who changed his address an inquiry as to his position, etc. This system, suggested by the ENAR Secretary has produced excellent results. Sometimes ballots are sent to student members inadvertently and a reminder was made that they are not entitled to vote. Four general mailings to the members of WNAR have been made this year The postage cost is about $6 a mailing, but this figure may go up as a result of the Secretary's office being moved to Washington State University, Pullman, Washington.

The Treasurer, Bernice Brown, gave her report. WNAR now has 164 members, 8 of them students, an overall gain of 14 from last year. As of August 20, 1960, there was $445.25 on hand. The operating expenses balanced out the income for this year. It was brought out that much of the money in the treasury was accumulated during past administrations when much of the cost of printing and mailing was not born by the Society. WNAR receives $1 for every member, $10 for each sustaining member, and nothing from student members. The Treasurer stated that perhaps a working capital of $200 would be sufficient in the treasury, declaring $200 to be surplus.

The Nominating Committee made its report. Two positions on the Regional Committee are now open because of the expiration of the terms of Douglas Chapman and Donald Wohlschlag. The names submitted by the Nominating Committee were Donald Owen, New Mexico; Lincoln Moses, California; Marion Sandomire, California; and Douglas Chapman, Washington. No nominations were made from the floor. The vote will be taken by a mail ballot.

No action was reported by the Relationship of ASA and the Biometric Society Committee during the past year by Marion Sandomire. The By-laws of the region are being revised by William Taylor and will be submitted soon to the Regional Committee. The possibility of having a president-elect was discussed. At present the President is elected for two years, in order that he may be more experienced in the position. Several alternatives were proposed:

1. The presidency be made a one-year position. Then we would have a president-elect every year. The president-elect would act as a program chairman and would in addition receive copies of important letters from the officers and the Regional Committee.
2. On alternate years, a president-elect would be elected.
3. Leave as is.

It was pointed out that the need for a president-elect might become greater as the membership increased. It was suggested that this matter be considered by the Regional Committee and be submitted to the membership in a mail ballot.

Douglas Chapman moved and Calvin Zippin seconded the following motion: The By-laws may be amended by a two-thirds vote of members present at any annual meeting. Changes in the By-laws may be initiated by the Regional Com-

mittee and the By-laws amended by a majority of members voting in a mail ballot. This motion was passed by a unanimous vote.

Suggestions for the use of the surplus fund (about $200) in the treasury were:

1. Give prizes for the best student paper presented at an annual meeting (it was mentioned that this was tried a couple of years ago, but that students did not present any papers).
2. Do not use the money.
3. Send bound volumes of *Biometrics* to foreign universities.
4. Pay students' dues.
5. Pay the expenses of a speaker at the annual meeting.
6. The funds should be used to encourage interest in the society.
7. They could be used to promote membership (it was pointed out that new members' dues would increase the treasury's surplus).
8. Prizes could be given to the member bringing in the most new members.
9. A year's subscription could be given to outstanding students.

No agreement could be reached, so the Regional Committee will debate the issue by mail.

Two possible meeting places for the 1961 Annual Meeting were discussed. These were the meeting of the Pacific Division A.A.A.S. at the University of California, Davis, June 12–17, 1961 and the IMS Meeting at the University of Washington, Seattle, in August (later information indicates that this may be in June). A majority voted for the Seattle meeting.

The purpose of the program at the Annual Meeting was discussed. Should the program aim at a specific purpose, or should the papers be an expository review aimed at applied statistics? There was very little comment.

William Taylor announced that he would be attending a meeting in the East with representatives of other societies to consider the possibility of a federation of statistical societies, besides other purposes.

The meeting adjourned at 2:10 P.M.

Those present at the meeting were Abramson, Becker, Bennett, Brown, Chapman, Hopkins, Massey, Mode, Nash, Nicholson, Russell, Sandomire, Taylor, Vaughan, and Zippen.

NOTE ON ELECTION

Douglas G. Chapman and Marion M. Sandomire were elected to the Regional Committee for 1961–1963.

CHANGES IN MEMBERSHIP

(October 1, 1960–January 15, 1961)

Changes of Address

Miss Margaret F. Allen, Department of Biometrics, School of Aviation Medicine, USAF, Brooks Air Force Base, Texas, U. S. A.

Dr. David W. Alling, Institute Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland, U. S. A.

Professor Maurice S. Bartlett, Department of Statistics, University College, London W. C. 1, England.

Prof. Dr. Eduard Batschelet, 2500 Q Street N.W., Washington, D. C., U. S. A.

Mr. Rainald K. Bauer, Kolner Str. 228a, Dusseldorf, Germany.

Dr. Gilbert W. Beebe, National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington 25, D. C., U. S. A.
Dr. G. E. P. Box, Mathematics Research Center, U. S. Army, University of Wisconsin, Madison 6, Wisconsin, U. S. A.
Dr. David Bruce, Box 4059, Portland, Oregon, U. S. A.
Dr. Joseph G. Bryan, 11 Newport Avenue, W. Hartford, Connecticut, U. S. A.
Mr. Walter E. Cole, Division of Forest Insect Research, U. S. Forest Service, Ogden, Utah, U. S. A.
Mr. Jerry Cornfield, National Institutes of Health, Bethesda, Maryland, U. S. A.
Dr. Paul M. Denson, Deputy Commissioner of Health, 125 Worth Street, New York 13, N. Y., U. S. A.
Prof. Benjamin Epstein, 768 Garland Drive, Palo Alto, California, U. S. A.
Dr. Robert Flamant, 11, rue Bouille, Fontenay—Aux—Roses (Seine) France.
Dr. William A. Glenn, 906 King Street, Cary, North Carolina, U. S. A.
Prof. John Gurland, U. S. Army Research Center, University of Wisconsin, Madison, Wisconsin, U. S. A.
Dr. Thomas J. Haley, 3401 Woodcliff Road, Sherman Oaks, California, U. S. A.
Dr. Sudako Hayase, 1038 Fifth Street, Santa Monica, California, U. S. A.
Prof. Dr. Ottokar Heinisch, Grunderstr. 28, Berlin—Grunau, Germany.
Dr. Henry Hopp, Agricultural Attache—Bogota, c/o U. S. Department of State, Washington 25, D. C., U. S. A.
Professor Gwilym Jenkins, Department of Mathematics, Imperial College, London, S.W. 7, England.
Dr. S. Karatas, Department of Animal Husbandry, University of Ataturk, Erzurum, Turkey.
Dr. Eileen B. Karsh, Department of Psychology, University of Pennsylvania, Philadelphia, Pennsylvania.
Mr. Charles Kiss, La Menitre, (Maine-et-Loire) France.
Mr. Gary F. Krause, 1110 Kentwood Drive, Blacksburg, Virginia, U. S. A.
Mr. William T. Lewish, 2109 Wildwood Drive, Woodland Park, Wilmington 5, Delaware, U. S. A.
Mr. Donald G. MacEachern 608 Third Avenue, S. E., Minneapolis 14, Minnesota, U. S. A.
Mr. John W. Mayne, Van Zaeckstraat 49, The Hague, Netherlands.
Mr. Jean Mothes, 13, boulevard des Invalides, Paris 7e, France.
Mr. Clifford A. Myers, 2069 N. Navajo, Flagstaff, Arizona, U. S. A.
Dr. Wesley L. Nicholson, 1215 E. 3rd, Moscow, Idaho, U. S. A.
Dr. Fernando Orozco-Pinan, Explotaction "El Encin" Alcala de Henares (Madrid) Spain.
Dr. Laurence M. Potter, Department of Poultry Husbandry, Virginia Polytechnic Institute, Blacksburg, Virginia, U. S. A.
Dr. D. R. Read, Cadbury Brothers Limited, Bournville, Birmingham, England.
Mr. A. H. L. Rotti, Av. Emile Verhaeren 70, Gentbrugge, Belgium.
Mlle. Claude Rouquette, 3, rue Saint-Charles, Paris 15, France.
M. Jean Soule, 30 avenue Saint-Laurent c. 34 (Orsay) Seine-et-Oise, France.
Mr. John J. Sowinski, Allstate Insurance Company, 7447 Skokie, Blvd., Skokie, Illinois, U. S. A.
Prof. David F. Votaw, Jr., 6 Fairlane Terrace, Winchester, Massachusetts, U. S. A.
Mr. Jerry Warren, Department of Horticulture, University of Nebraska, Lincoln 3, Nebraska, U. S. A.

Mr. Francis R. Watson, 1415 Winding Lane, Champaign, Illinois, U. S. A.
Mrs. Sandra S. White, 535 E. 72nd Street, New York 21, N. Y., U. S. A.
Mr. Amador D. Ynigues, Institute of Statistics, P. O. Box 5457, Raleigh, North Carolina, U. S. A.
Dr. Sydney S. Y. Young, 68 Barker Road, Strathfield, N.S.W., Australia.

New Members

At Large

Mr. Pedro Eliz M. Revello, Instituto Venezolano Petroquim, Centro Simon Bolivar, Caracas, Venezuela.

Brazil

Mr. Joassy de Paula Neves Jorge, Instituto Agronomico Caixa Postal 28, Campinas S.P., Brazil.

France

M. Pierre Lossois, 120 bis avenue de Verdun, Issy-les-Moulineaux (Seine) France.

Germany

Dipl. G. Enderlein, Karl-Marx-Str. 31, Klein Wenzleben bei, Magdeburg/DDR, Germany.
Mr. Werner Haufe, Sophienstr. 21, Einbeck/Hann., Germany.
Prof. Dr. A. Maede, Eichenweg 5, Halle/Saale, Germany.
Mr. Dieter Rasch, Fritz Reite Str. 22, Rostock, Germany.
Dr. Ernst Weber, Windhalmweg 36, Stuttgart-Plieninger, Germany.
Doz. Dr. Hermann Witting, Dreikonigstrasse 9, Freiburg i. Br., Germany.

Italy

Dott. Giuseppe Agnese, Istituto di Igiene dell'Universita, via Pastore 1, Genova, Italy.
Dr. Giancarlo Chisci, Stazione Sperimentale di Praticoltura, Viale Piacenza 25, Lodi, Milano, Italy.
Dr. Maurizio Turri, Viale O. P. Vigliano 17, Milano, Italy.

Western North American Region

Mr. Peter A. Dawson, Department of Genetics, University of California, Berkeley 4, California, U. S. A.
Dr. Olive Jean Dunn, School of Public Health, University of California, Los Angeles 24, California, U. S. A.
Prof. Robert F. Fagot, Department of Psychology, University of Oregon, Eugene, Oregon, U. S. A.
Dr. Robert Macey, Department of Physiology, University of California, Berkeley 4, California, U. S. A.
Mr. Prem Singh Puri, 1845 Hearst Avenue, Berkeley 3, California, U. S. A.
Mr. Kurt Sittman, Animal Husbandry Department, University of California, Davis, California, U. S. A.
Mr. Albert R. Stage, 157 South Howard Street, Spokane 4, Washington, U. S. A.

NEWS AND ANNOUNCEMENTS

Members are invited to transmit to their National or Regional Secretary (if members at large, to the General Secretary) news of appointments, distinctions, or retirements, and announcements of professional interest.

EDITORIAL NOTE

The general objective of *Biometrics* is to promote and to extend the use of mathematical and statistical methods in pure and applied biological sciences. This objective has been broadly interpreted in editorial decisions and this is proper. However, it is believed also that mathematicians and statisticians contributing to *Biometrics* have an obligation to present their work so that the natures of the problems in the biological sciences to which the methods apply are clearly understood by those who may profit by the use of the methods. Similarly, biologists should explain their problems so that their needs and methods are clearly understood by the mathematician and statistician. While these requirements may not be easy to meet, direct consideration of them should greatly increase the value of *Biometrics* to all members of the Biometric Society. Careful attention to introductions of papers, including formulation of problems and models, with skillful selection of examples would be helpful. When possible, algebraic and mathematical discussions should be placed in appendices to papers in order that they do not detract from the emphasis on the problem areas and the readability of papers.

MEETINGS OF E. N. A. R.

The Eastern North American Region will meet jointly with the Institute of Mathematical Statistics and the American Statistical Association on April 20, 21, and 22, 1961, at Cornell University. Titles and abstracts, the latter in duplicate in the form published in *Biometrics*, of contributed papers for ENAR should be sent to Dr. Erwin L. LeClerg, Biometrical Services, Plant Industry Station, Beltsville, Maryland.

In 1961, ENAR will also meet jointly with the American Institute for Biological Sciences at Purdue University and with the American Statistical Association in New York City.

MEETING OF W.N.A.R.

The Western North American Region will meet jointly with the Institute of Mathematical Statistics in June, 1961, at the University of Washington.

UNIVERSITY ANNOUNCEMENTS

THE CATHOLIC UNIVERSITY OF AMERICA

The Statistical Laboratory of the Catholic University of America has been awarded a grant by the National Institutes of Health for training in the field of Biometry.

The stipends for first-year graduate students are $2250 plus tuition; family allowances for dependents and annual increases are provided.

The students will pursue the same general program as other students in mathematical Statistics. They will participate in the consulting activities of the laboratory and will be required to attend some courses in the biological sciences or other fields relevant to the study of biometry.

In addition to the grants in biometry, there are also fellowships under the National Defense Education Act available. Some appointments to graduate assistantships and research assistantships will also be made.

The Statistical Laboratory of the Catholic University of America is also expanding its activities into the areas of biomathematics and biometry. A training program and consulting service are being organized. Professor Edward Batschelet (on leave from the University of Basel, Switzerland) was appointed Visiting Professor in this program for the academic year 1960–61. Professor Harold Bergstrom of the Institute of Applied Mathematics of Chalmers Institutes of Technology (Goteborg, Sweden) was appointed Visiting Professor for the academic year 1960–61. He will primarily be engaged in research in probability theory. Professor D. Dugue of the Sorbonne (Paris, France) and Dozent T. E. Dalenius of Stockholm University are expected to visit Catholic University during the spring term 1961.

Requests for further information and application forms should be addressed to Professor Eugene Lukacs, Director, Statistical Laboratory, The Catholic University of America, Washington 17, D. C.

IOWA STATE UNIVERSITY

The National Science Foundation will sponsor a Summer Institute for College Teachers of Statistics at Iowa State University for the 11-week period from June 5 through August 18, 1961. The Departments of Statistics of three other universities, Kansas State, Utah State and the University of Wyoming, are cooperating with Iowa State's statistical center in presenting this institute.

Financial support in the form of stipends, dependency allowances and travel allowances will be awarded to 50 eligible applicants. All American college and university teachers who are, or who during the 1961–62 academic year will be, required to teach one or more courses in statistics as part of their regular assignments are eligible for consideration.

The institute is planned to provide additional basic training in statistics for present and prospective teachers who, though well-grounded in other fields, have limited backgrounds in statistics. Also it will provide more advanced courses and seminars designed to keep college and university teachers abreast of new developments.

Courses are scheduled in Statistical Methods, Theory of Statistics, Experimental Design, Survey Designs, Topics in Foundations of Probability and Statistics, and Intermediate Applied Decision Theory. In addition, an opportunity will be provided for those interested to observe a demonstration class in Principles of Statistics at the undergraduate level. The faculty will include the institute director, Dr. T. A. Bancroft, Director of the Iowa State University Statistical Laboratory and Head, Department of Statistics; Dr. R. J. Buehler, Associate Professor of Statistics, Iowa State University; Dr. H. T. David, Associate Professor of Statistics, Iowa State University; Dr. H. C. Fryer, Head of the Department of Statistics and Statistical Laboratory Director, Kansas State University; Dr. H. O. Hartley, Professor of Statistics, Iowa State University; the Institute Associate Director, Dr. D. V. Huntsberger, Associate Professor of Statistics, Iowa State University; and Dr. R. L. Hurst, Head of the Department of Applied Statistics and Statistical

Laboratory Director, Utah State University. Guest lecturers will present a series of special seminars.

Requests for information or application forms should be addressed to: The Director, Summer Institute in Statistics, 102 Service Building, Iowa State University, Ames, Iowa.

The Department of Statistics at Iowa State University will offer also eight applied courses in statistical theory and methods in its two 1961 summer sessions. These courses are planned primarily for graduate students or research workers with limited mathematical backgrounds who wish to use statistical techniques intelligently for application to other fields. In addition, a course on special topics in theoretical or applied statistics may be studied at the graduate level. Senior staff members will be available during most of the summer for consultations on research or special problems.

Students may register for either or both of the six-week summer sessions: June 5–July 12 and July 12–August 18. The complete list of statistics offerings for the first session is as follows: Stat. 401, "Statistical Methods for Research Workers "(at the level of Snedecor's *Statistical Methods*); Stat. 447, "Statistical Theory for Research Workers" (mainly theory of experimental statistics at the level of Anderson and Bancroft's "*Statistical Theory in Research*"; Stat. 411, "Experimetnal Designs for Research Workers," Stat. 599, "Special Topics;", Stat. 599A1, "Topics in Foundations of Probability and Statistics;" and Stat. 699, "Research." In the second session will be offered Stat. 402, a continuation of 401, Stat. 448, a continuation of 447; Stat. 421, "Survey Designs for Research Workers;" Stat. 599, Stat. 599A2, "Intermediate Applied Decision Theory (at the level of Blackwell and Girshick, *Theory of Games and Statistical Decisions*), and Stat. 699.

JOHNS HOPKINS UNIVERSITY

Beginning next September, the Department of Biostatistics at The Johns Hopkins University will offer an expanded program of study and research leading to Master of Science and Doctor of Science degrees. The curriculum has been modified by increasing the scope of the basic courses in statistical theory and statistical methods and by the addition of specialized courses including least squares and regression, stochastic processes, nonparametric methods, sampling and survey methods, biological assay, design of experiments and digital computer programming. These changes reflect a realization of the need for more intensively trained statisticians in the areas of biology, medicine and public health, and they are the direct result of the increasingly important role played by mathematics and statistics in all areas of scientific research.

The new program was made possible in part by the recent addition to the department of Drs. Allyn W. Kimball and David B. Duncan who together with Drs. Helen Abbey, Earl Diamond, John J. Gart and Margaret Martin form the permanent staff. In September, 1961, Dr. Norman T. J. Bailey of Oxford University will join the staff as visiting professor and will teach the course in stochastic processes. Additional appointments may be announced shortly.

The department has a limited number of liberal fellowships available, and interested students are invited to write to the Chairman, Department of Biostatistics, 615 North Wolfe Street, Baltimore 5, Md. for further information.

PURDUE UNIVERSITY

There will be three intensive courses in the general areas of statistical methods

and quality control, design of experiments, and operations research at Purdue University this summer.

The course in Statistical Methods and Advanced Quality Control has been given at Purdue annually since 1947, being most recently revised in 1960. This course is designed for those who have had the equivalent of one of the intensive courses in statistical quality control given during and after the war, and who want to learn more about the statistical approach to industrial and research problems.

Topics to be studied during the ten-day quality control course are Significance Tests and Confidence Intervals, Significance of Differences, Linear Correlation and Regression, Single Sampling for Measurements, Sequential Sampling for Measurements, Multiple Correlation, and Analysis of Variance. Instructors include Profs. Irving W. Burr, the course director, and Charles R. Hicks, both of Purdue, Cecil C. Craig of the University of Michigan and Gayle McElrath of the University of Minnesota. The dates for this course are September 5–15.

The second course is on Design of Experiments and is for statisticians, quality control personnel, engineers, and others concerned with planning, analyzing, and interpreting the results of industrial experiments. The dates for this course are June 7–17. This will be the third year this course has been offered.

Professor Hicks, of the mathematical and statistical staff, the course director, emphasizes that this advanced course is for persons who have had previous statistical training, including work on tests of hypotheses, linear correlation, and at least an introduction to analysis of variance.

Topics included in the short course are Review of Analysis of Variance, Principles of Experimental Design, Variance Component Analysis, Randomized Blocks and Latin Squares, Factorial Experiments, Split Plot Designs, Confounding in Factorial Experiments, Incomplete Block Designs, Fractional Replications, and Introduction to Evolutionary Operations (EVOP).

In addition to Professor Hicks, instructors will include Prof. Clyde Y. Kramer, Virginia Polytechnic Institute, and Professor McElrath. Enrollment will be limited to a maximum of 25–30.

The third ten-day short course is on The Mathematical Techniques of Operations Research which will be offered at Purdue University for the second time this summer on June 5–15.

The course has been designed for statisticians, quality control analysis, engineers, and other technical personnel in industrial and management positions. Emphasis will be placed on the mathematical techniques of operations research and the application of these methods to current industrial and military problems.

These methods involve the construction of mathematical models representing the operation of industrial management or a military organization, and suggest the best solutions to problems involved. Among the topics to be discussed during the course are inventory control models, waiting line models, linear programming, simplex method, transportation methods, production scheduling models, search theory, cost-effectiveness studies, and systems analysis.

Instructors for the short course are Prof. Paul Randolph of Purdue, who is the short course director, Albert Madansky, of the RAND Corporation, and Prof. Bernard Lindgren, of the University of Minnesota. Enrollment in this course will be limited.

All three courses are sponsored jointly by the Statistical Laboratory and the Division of Adult Education at Purdue. Further information about any of the courses may be obtained by writing to the Division of Adult Education, Purdue University, Lafayette, Indiana.

SOUTHERN METHODIST UNIVERSITY

The National Science Foundation has awarded Southern Methodist University a grant of $26,400 to conduct a basic study of the feasibility of making the new Science Information Center at SMU a regional scientific and technical information center serving the needs of Southwestern industry and higher education.

Dr. William J. Graff, Jr., chairman of the SMU Department of Mechanical Engineering, is principal investigator for the study. He is assisted by Sam G. Whitten, SMU Science Librarian.

The building to house the new Science Information Center, a gift of local industrialists, is under construction and is scheduled for completion next August. A million dollar structure consisting of 80,000 sq. ft. on four floors, it will have space for half a million books. It will serve the SMU faculty and student body as well as the new Graduate Research Center. Space is provided in the building for administrative offices of the Graduate Research Center, whose director is Dr. Lloyd Berkner; for the SMU Map Library and Herbarium; and for the DeGolyer Geology Collection, in addition to the general document collections in science, mathematics, and engineering.

The study sponsored by the National Science Foundation is scheduled for completion in May, 1961. It will be based to a large extent on personal interviews and questionnaires aimed at the scientists and technicians who are engaged in research in the Southwest. An attempt will be made to find out what kind of information the research people need and in what subjects.

Also involved in the study are visits to and detailed studies of existing scientific information centers and an economic study of the area done by business economists.

The investigators expect to reach many research workers by questionnaires sent through local professional and scientific and technical societies, and will ask for employers aid in setting up personal interviews with research workers.

UNIVERSITY OF MINNESOTA

A special summer program of statistics in the Health Sciences will be held from June 13 to July 28, 1961 at the University of Minnesota. Courses in diverse areas of statistics at elementary and advanced levels will be given. Experts from around the nation will be teaching. Stipends are available to qualified students. For further information write to Biostatistics, 1226 Mayo, University of Minnesota, Minneapolis 14, Minnesota.

VIRGINIA POLYTECHNIC INSTITUTE

The 1961 session of the Southern Regional Graduate Summer Session in Statistics will be held at the Virginia Polytechnic Institute, Blacksburg, Virginia, from June 15 to July 22, 1961.

The Virginia Polytechnic Institute, Oklahoma State University, North Carolina State College, and the University of Florida have agreed to operate a continuing program of graduate summer sessions in statistics to be held at each institution in rotation. The program was instituted at Virginia Polytechnic Institute in the Summer of 1954.

The 1961 session, like previous sessions under this program, is intended to serve: 1) teachers of statistics and mathematics; 2) professional workers who want formal training in modern statistics; 3) research and engineering personnel who want intensive instruction in basic statistical concepts and modern statistical meth-

odology; 4) Public Health statisticians who wish to keep informed about advanced specialized theory and methods; 5) prospective candidates for graduate degrees in statistics; and 6) graduate students in other fields who desire supporting work in statistics.

The session will last six weeks and courses will carry five quarter hours of credit. Not more than two courses may be taken for credit at any one session. The summer work in statistics may be applied as residence credit at any of the cooperating institutions, as well as certain other universities, in partial fulfillment of the requirements for a graduate degree. The program may be entered at any session, and consecutive courses will follow in successive summers so that it would be possible for a student to complete the course work in statistics for a Master's degree in three summers. Students must satisfy the remaining requirements for course work and thesis at the institution where they are to be admitted to candidacy. The advanced courses may be accepted as part of the Ph.D. program of the participating institutions.

A limited number of fellowships will be available for applicants from certain specialized areas. Doctoral courtesy will be honored for those holding Ph.D. or M.D. degrees.

The courses to be offered in statistics in 1961 at the Virginia Polytechnic Institute are as follows: Statistical Methods, Sampling Theory; Applied Statistics for Engineers and Physical Sciences; Theory I, Probability; Theory II, Statistical Inference; Theory III, Theory of Least Squares; Principles and Practices of High Speed Computing (enrollment limited to 14); Non-parametric Methods; and Multivariate Methods.

A number of courses in advanced mathematics will be available during the Summer Session. For a complete listing please consult the University timetable. A series of Colloquia involving recent developments in statistical theory and methods will be conducted during the special Summer Session.

Requests for application blanks for the summer session and for fellowships should be addressed to Dr. Boyd Harshbarger, Head, Department of Statistics, Virginia Polytechnic Institute, Blacksburg, Virginia.

CONTINENTAL CLASSROOM

Probability and Statistics, a nationally televised college-credit mathematics course, will be offered on the second semester of Continental Classroom beginning January 30, 1961.

Presented by Learning Resources Institute in cooperation with the Conference Board of the Mathematical Sciences, and telecast in color and black-and-white by the National Broadcasting Company, the course will be taught by Professor Frederick Mosteller, Chairman, Department of Statistics, Harvard University, and Professor Paul C. Clifford, Professor of Mathematics, Montclair (N. J.) State College.

More than 300 colleges and universities are expected to offer the televised course for college credit. It will be carried by 170 stations throughout the nation, from 6:30 to 7 a.m. Monday through Friday in each time zone.

NEW JOURNALS

Journal of the Forensic Science Society

Stuart S. Kind is the editor of a new journal, *The Journal of the Forensic Science Society* with editorial office c/o Rossett Holt, Pennal Ash Road, Harrogate, York-

shire, England. Papers on biometry, especially in relation to human individuality, classification, and identification systems, will be welcomed.

Crop Science

Crop Science is the name of the new research journal which will appear in February 1961 as the official publication of the Crop Science Society of America, an affiliate of the American Society of Agronomy.

This new, bimonthly journal will carry research reports on breeding, genetics, physiology, ecology, and management of field crops, pastures, ranges, and turfgrasses from crop scientists in the U. S., Canada, and other countries.

Crop Science will be a companion publication to *Agronomy Journal*, the official organ of the ASA. It will alternate in publication dates with the *Journal* and will carry the articles (formerly publishable in the *Journal*) of direct interest to workers in the above-mentioned areas of research. *Agronomy Journal* will continue to carry the articles of wider agronomic scope—of interest to both crop and soil scientists, seed and weed technologists, plant pathologists, agricultural meteorologists, and others.

Publication of research reports in *Crop Science* will be open to members of the Crop Science Society—with joint membership in the American Society of Agronomy. Detailed information on publication in or subscription to *Crop Science* or *Agronomy Journal* or both may be obtained from the American Society of Agronomy, 2702 Monroe Street, Madison 5, Wisconsin.

TRAVEL GRANTS FOR ATTENDANCE AT THE INTERNATIONAL CONGRESS OF MATHEMATICIANS

Travel grants will be made to a number of mathematicians who wish to attend the International Congress of Mathematicians in Stockholm, on August 15–22, 1962. It is hoped that funds available through various sources may provide travel assistance for a considerable number of mathematicians.

There will be a greater effort than in the past to give aid to younger people. As grants will be made only to those who have filed applications, it is urgent that any who wish to receive a grant should fill out and file an application. Younger people are urged to file applications so that their cases can be considered. Applications can be obtained from the Division of Mathematics, National Academy of Sciences, National Research Council, Washington 25, D. C. by requesting an application for a travel grant to the 1962 International Congress.

The deadline for filing of applications is November 1, 1961, and an attempt will be made to announce the grants by January 1, 1962.

Awarding of grants will be made only to those persons whose applications have been received, in good order, by November 1. The selection will be made by a committee consisting of the regular Committee on Travel Grants of the Division of Mathematics of the National Academy of Sciences—National Research Council enlarged to include representatives of societies affiliated with the Division and representatives of various governmental agencies.

NEWS ABOUT MEMBERS

Laurence H. Baker is presently employed by Hy-Line Poultry Farms as a geneticist in Des Moines, Iowa.

David Bruce is Chief of Division Forest Fire Research, Pacific Northwest

Forest and Range Experiment Station, USDA. He formerly held the same position at the Southern Forest Experiment Station.

Martha W. Dicks is presently Assistant Professor of Human Nutrition at Montana State College.

Charles W. Dunnett was awarded a D.Sc. degree in statistics on completion of a two-year period of research at the University of Aberdeen, Scotland, under Dr. D. J. Finney, F.R.S. The title of his thesis was "The Statistical Theory of Drug Screening." He has now returned to his position as Head of the Statistical Design and Analysis Department at the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York.

Lincoln J. Gerende is presently Instructor in Biostatistics, Department of Epidemiology and Public Health, Medical School, Yale University.

Leo A. Goodman is a Visiting Professor of Mathematical Statistics and Sociology at Columbia University during 1960–61 on leave from his position at the University of Chicago.

John Gurland, on leave from Iowa State University, is presently employed at the Mathematics Research Center of the University of Wisconsin in Madison, Wisconsin.

James A. Hagans of the Department of Preventive Medicine and Public Health of the University of Oklahoma has recently received his Ph.D. degree from that institution.

Carl E. Hopkins is now special consultant (Air Pollution Medical Studies) to the School of Public Health, UCLA.

Leo Kats has returned to his position as Head of the Department of Statistics, Michigan State University. He was on leave of absence serving as Scientific Liaison Officer for the Office of Navy Research in London, England, covering statistics and probability in Europe.

George H. Kennedy is presently employed by the Department of Health, Education and Welfare, U. S. Public Health Service in Bethesda, Maryland. He was formerly at the Biological Laboratories of the Department of Defense at Fort Detrick, Maryland.

John R. Kinzer has recently returned to his position of Professor of Psychology at Ohio State University, Columbia. He had been on a two-year leave of absence to work at the System Development Corporation, Santa Monica.

Gary F. Krause has given up his post as Instructor in Statistics at Kansas State University to become a full time graduate student in Statistics at the Virginia Polytechnic Institute at Blacksburg, Virginia.

Dr. Kuo Hua Lee has taken a position as an Associate Professor of Biostatistics in the University of Oregon Dental School, Portland.

William T. Lewish has taken a position as Special Service Engineer for the E. I. DuPont de Nemours and Co. in Wilmington, Delaware.

Alexander M. Mood formerly president of General Analysis Corporation became Vice-President of C-E-I-R, Inc. and Manager of the Los Angeles Research Center of C-E-I-R, when General Analysis Corporation merged with C-E-I-R.

Wesley L. Nicholson is on a four-month-special assignment as Professor of Mathematics at the University of Idaho. His permanent post is senior statistician for the General Electric Company in Richland, Washington.

L. M. Potter, formerly Research Associate in the Department of Poultry Science at the University of Connecticut, is now Associate Professor in the Department of Poultry Husbandry at the Virginia Polytechnic Institute at Blacksburg, Virginia.

Mr. J. N. K. Rao, an advanced graduate student in Statistics at Iowa State University, has been selected as the recipient of the George W. Snedecor Award in Statistics, which consists of a cash prize of $25.00, a year's membership in the Institute of Mathematical Statistics and a year's subscription to the *Annals of Mathematical Statistics*.

Maynard W. Shelly, II, formerly a psychologist in the Office of Naval Research is now a mathematician in the Logistics and Mathematical Statistics Branch of ONR.

John H. Smith is a Visiting Professor at the University of Chicago during the year. He is on sabbatical leave from the American University.

Jerry Warren is presently Assistant Professor in the Horticulture Department of the University of Nebraska. He was formerly with the Vegetable Crops Department of Cornell University.

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For further information, please contact:
AMERICAN STATISTICAL ASSOCIATION
1757 K Street, N. W., Washington 6, D. C.

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